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Radical Reduction of Cyclohexanones, Sequential Ring-closing Metathesis and Radical Cyclization, and Synthetic Studies Related to CP-225,917

©

by

Hua Cheng

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **Radical Reduction of Cyclohexanones, Sequential Ring-closing Metathesis and Radical Cyclization, and Synthetic Studies Related to CP-225,917** submitted by **Hua Cheng** in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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6/20/03

To my Family

ABSTRACT

The first Chapter of this thesis describes a method for radical reduction of cyclohexanones that leads to preferential formation of equatorial alcohols. A report of the method is in press (Clive, D. L. J.; Cheng, H. *Synth. Commun*. **2003**). The procedure involves converting a cyclohexanone into a spiro[4H-3,1-benzoxaselenin-2,1'-cyclohexan]-4-one (e.g. **26.1**) by treatment with 2-hydroselenobenzoic acid in the presence of $BF_3.OEt_2$, followed by reduction with Bu_3SnH in the presence of a radical initiator. This procedure gives a mixture of esters which affords the alcohol on mild hydrolysis. The alcohol is a mixture of axial and equatorial isomers, with the latter predominating.

The second Chapter of this thesis reports the development of a method for sequential ring-closing metathesis and radical cyclization. The procedure constitutes an efficient route to a wide range of bicyclic compounds, and has been published (Clive, D. L. J.; Cheng, H. *J. Chem. Soc., Chem. Comm*. **2001**, 605-606). In essence, the method involves forming a substrate for ring closing metathesis (e.g. **26.1**, Chapter 2 numbering) in which the radical trigger – a phenylseleno group – is already present. After ring closing metathesis, the product is correctly constituted for radical cyclization, which affords a bicyclic compound. The finding that the phenylseleno group is

compatible with the Grubbs catalyst shortens the route to the product of radical cyclization, as it avoids the steps otherwise needed to convert a protected hydroxyl into a homolyzable group.

The third part of this thesis describes studies towards the synthesis of the natural product CP-225,917. To this end, a 2.2.1-bicyclic compound (**47.9**, Chapter 3 numbering) was prepared carrying suitable substituents, in particular the (*E*)-6-octenyl side chain of the natural product. The route involved the synthesis of 2.2.1-bicyclic compounds in which the C(7) substituent is *anti* to the substituent that is elaborated into the octenyl side chain. In early experiments where this situation did not prevail, homologation of the octenyl side chain was thwarted by steric factors.

ACKNOWLEDGMENTS

I would like to express my gratitude to Dr. D. L. J. Clive for his constant support and encouragement during the course of my Ph.D. program, and for his assistance during the preparation of this thesis.

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Abbreviations

AIBN	2,2'-azobisisobutyronitrile
Boc	*t*-butyloxycarbonyl
Bu$_2$BOTf	dibutylboron trifluoromethanesulfonate
CBS	Corey-Bakshi-Shibata
Cy	cycohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	*p*-dibenzoquinone
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
EDC	2-(dimethylaminoethyl)propylcarbodiimide
FTIR	Fourier transform infrared
HMPA	hexamethylphosphoric triamide
Im	imidazole
LHMDS	lithium bis(trimethylsilyl)amide
m-CPBA	*m*-chloroperbenzoic acid
MAD	methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide)
Mes	mesityl
MOMCl	methoxymethyl chloride
MsCl	methanesulfonyl chloride
MsOH	methanesulfonic acid
NIS	*N*-iodosuccinimide

NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Pg	protecting group
Pmb	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
pyr	pyridine
RCM	ring-closing metathesis
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TBSCl	*t*-butyldimethylsilyl chloride
TBSOTf	*t*-butyldimethylsilyl trifluoromethanesulfonate
TES	triethylsilyl
Tf_2O	trifluoromethanesulfonic acid anhydride
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSOTf	trimethylsilyl triflate
TPAP	tetrapropylammonium perruthenate
TsCl	*p*-toluenesulfonyl chloride
TsOH	*p*-toluenesulfonic acid
UV	ultraviolet

Chapter 1

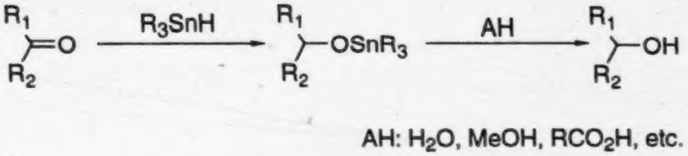
A Free Radical Method for Reduction of Cyclohexanones – Preferential Formation of Equatorial Alcohols

Introduction

The reduction of carbonyl compounds with hydride reagents is a well-established two-electron process that has been used extensively in organic synthesis.[1] The related free-radical reduction of carbonyl compounds is a potentially valuable one-electron alternative; however, the radical reaction is not nearly as well-developed as hydride reduction, and only a few papers have been published on the subject. In this introduction, some applications of radical reduction of carbonyl compounds using Bu_3SnH, SmI_2, and silanes are discussed.

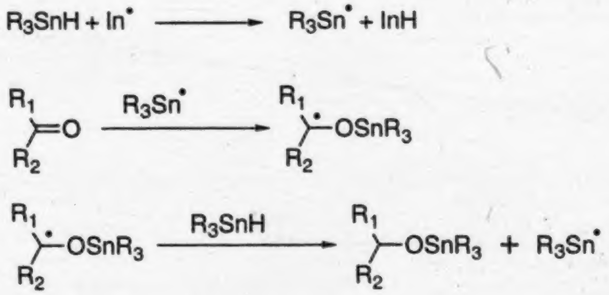
1. Reduction of Carbonyl Compounds Using Bu_3SnH

Hydrostannylation of carbonyl compounds gives rise to tin alkoxides (Scheme 1).[2] The resulting Sn-O bond can be cleaved by protonolysis with water, an alcohol or an acid.



Scheme 1

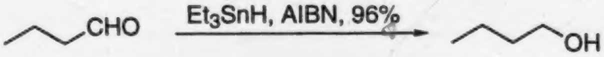
The hydrostannylation follows a radical pathway when initiated with AIBN or UV light, as outlined in Scheme 2.



Scheme 2

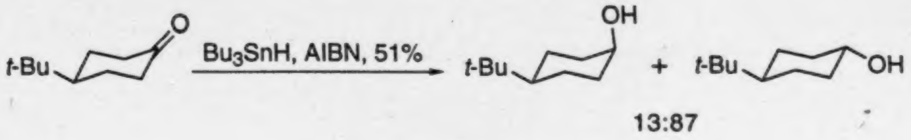
Upon treatment with an initiator, the tin hydride affords a tin radical; this adds to the carbonyl group to give a tin ketyl radical. The latter then abstracts hydrogen from R_3SnH furnishing a tin alkoxide.

AIBN-initiated radical reduction of butyraldehyde with Et_3SnH gave butanol in 96% yield (Scheme 3).[3] When Et_3SnH was replaced by Bu_3SnH, a similar result was obtained.[3]



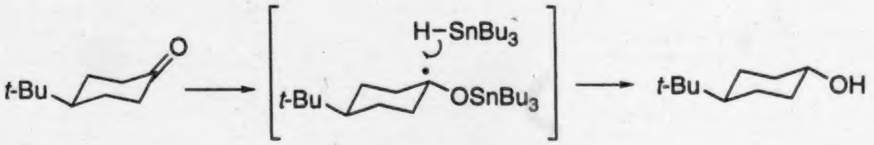
Scheme 3

Reaction of *t*-butylcyclohexanone with Bu_3SnH and AIBN



Scheme 4

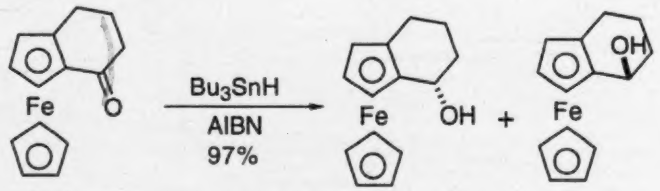
affords a 51% yield *t*-butylcyclohexanols (Scheme 4).[4] Because an axial approach of Bu_3SnH to radical intermediate **5.1** is favored, *trans*-*t*-butylcyclohexanol was obtained as the major product (Scheme 5).[4]



5.1

Scheme 5

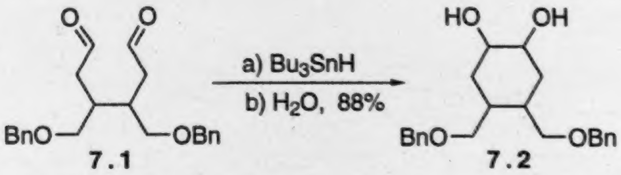
Reduction of ferrocenyl ketone **6.1** with Bn_3SnH and AIBN afforded predominantly the *endo* alcohol **6.2**, apparently due to steric approach control in the hydrogen transfer step (**6.2**:**6.3** = 87:13) (Scheme 6).[5]



6.1 **6.2** **6.3**

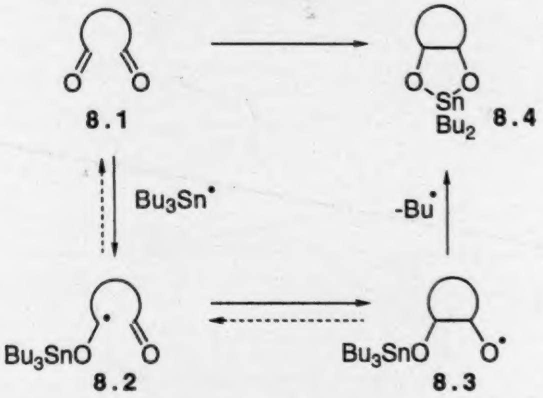
Scheme 6

In 1995, Fu reported an intramolecular pinacol coupling of dialdehyde **7.1** (see Scheme 7).[6] An aldehyde ketone (not shown) also reacted in the same way.



Scheme 7

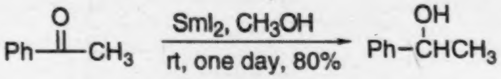
The proposed mechanism is shown in Scheme 8 for the dialdehyde reaction. Addition of tributyltin radical to the carbonyl group gave tin ketyl radical **8.2**, which attacked the other carbonyl, furnishing radical **8.3**. Addition of the oxygen-centered radical to tin formed the cyclic tin alkoxide **8.4** with release of a butyl radical.



Scheme 8

2. Reduction of Carbonyl Compounds Using SmI_2

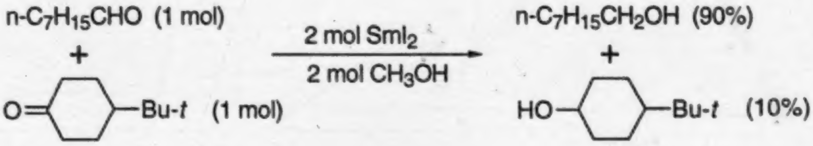
Reduction of carbonyl compounds with SmI_2 was first reported by Kagan and coworkers in 1980 (Scheme 9).[7]



Scheme 9

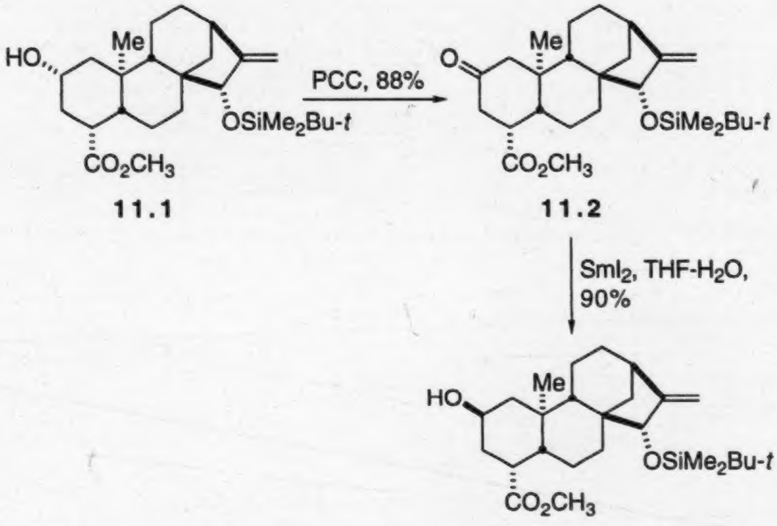
Acetophenone was reduced with 2 equiv. SmI_2 and 2 equiv. MeOH to give 1-phenylethanol in 80% yield.

SmI_2 is chemoselective for reduction of aldehydes in the presence of ketones, as shown by the experiment summarized in Scheme 10.[7]



Scheme 10

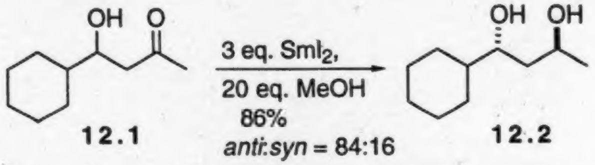
In Corey's synthesis of atractyligenin, alcohol **11.1** was



Scheme 11

oxidized to ketone **11.2** with PCC, and selective reduction of the ketone functionality in **11.2** with SmI_2 afforded the equatorial alcohol **11.3** in 90% yield (Scheme 11).[8]

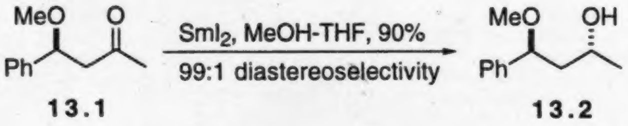
β-Hydroxy ketones are reduced with SmI_2 to give predominately *anti*-1,3-diols (Scheme 12).[9]



Scheme 12

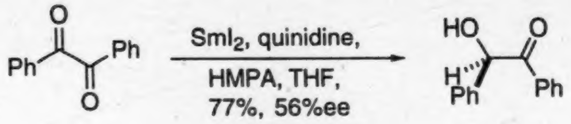
The mechanism of the reduction is obscure, but Keck has suggested it involves sequential one electron transfer processes to afford a samarium-bound carbanion.[9]

Diastereoselective reduction of β-alkoxy ketones to *anti*-1,3-diol monoethers, using SmI_2 has also been achieved by Keck's group (Scheme 13).[10]



Scheme 13

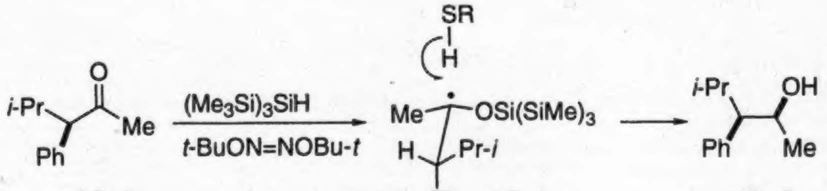
Finally, asymmetric reduction of benzil with SmI_2 in the presence of quinidine, has been reported to afford benzoin with moderate (56%) ee (Scheme 14). Quinidine behaves as a chiral protonating agent in this process.[11]



Scheme 14

3. Reduction of Carbonyl Compounds Using Silanes

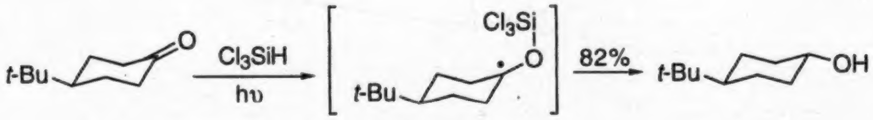
Addition of tris(trimethylsilyl)silyl radical to the chiral ketone **15.1** (Scheme 15) yielded radical **15.2**. This then abstracted hydrogen from $C_{12}H_{25}SH$ also present in the mixture to give predominantly the Cram product **15.3**.[12] The ratio of Cram to anti-Cram products was 12.6:1.



15.1 **15.2** **15.3**

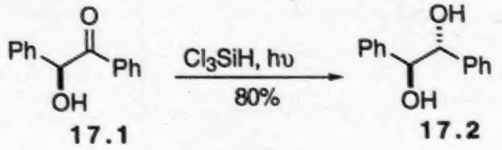
Scheme 15

Radical reduction of 4-*t*-butylcyclohexanone using the cheap reagent Cl_3SiH gave the equatorial alcohol as the major product (Scheme 16).[13]



Scheme 16

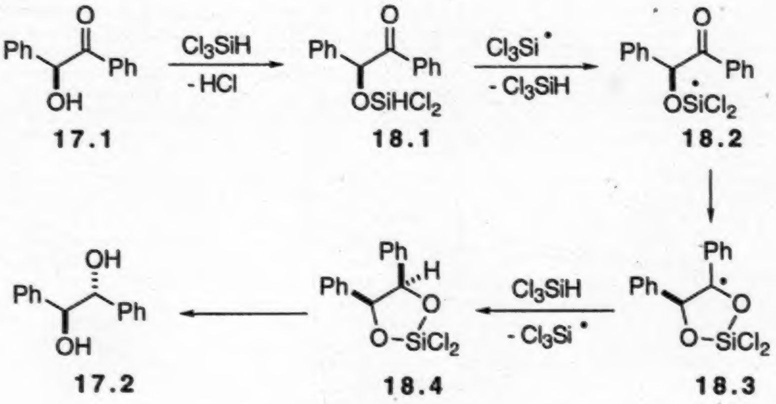
α-Hydroxy ketone **17.1** was reduced by Cl_3SiH to diol **17.2** with high diastereoselectivity – 38:1 in favor of the



Scheme 17

anti-diol (Scheme 17).[13]

The proposed mechanism of this reduction is outlined in Scheme 18.



Scheme 18

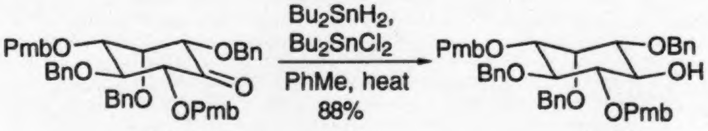
Reaction of **17.1** with Cl_3SiH yielded the α-silyloxy ketone **18.1**. Hydrogen atom abstraction from **18.1** by trichlorosilyl radical gave an electrophilic silyl radical **18.2**. This radical then attacked the electron-rich oxygen of the ketone to form the cyclic bis-silyl ether **18.3**. The five-membered ring incorporating the *O*-silyl ketyl radical provided a steric bias for stereoselective H-atom abstraction to produce **18.4**. Upon work up *anti*-**17.2** was obtained.

Conclusion

The above review shows that useful transformations can be effected by radical reduction of carbonyl groups, but the method has been very little used so far.

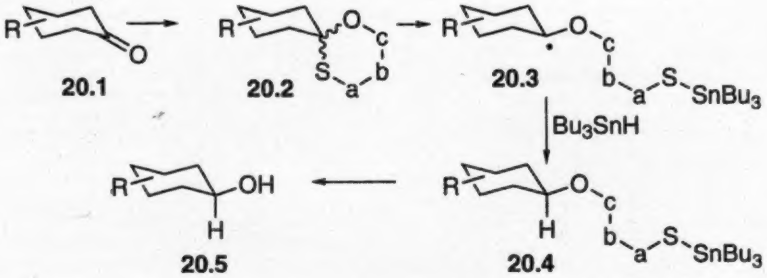
Results and Discussion

In connection with the synthesis of D-*myo*-1,3,4-inositol triphosphate[14] a reduction process was required to convert ketone **19.1** into the corresponding equatorial alcohol. Examination of several hydride reducing agents[14] ($NaBH_4$; MAD, DIBAL; MAD, *n*-Bu_4NBH_4; MAD, $NaBH_4$) showed that compound **19.1** was attacked equatorially to give the axial alcohol, and a number of ways were considered of reversing this tendency. Eventually a combination of reagents (Bu_2SnH_2, Bu_2SnCl_2) was found that worked very well[14] in this particular case (Scheme 19), but among the methods considered was generation of a radical from a derivative of type **20.2**, as summarized in Scheme 20.



19.1 **19.2**

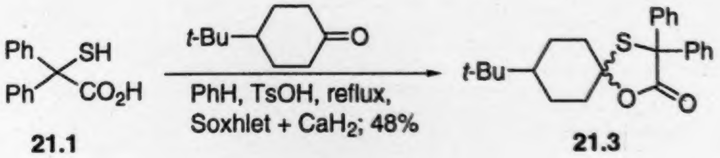
Scheme 19



Scheme 20

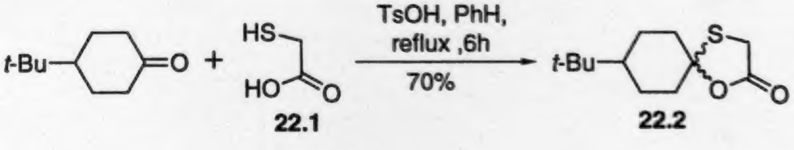
It was expected that reaction with a stannane would generate radical **20.3**, by analogy with the behavior of aldehyde-derived oxathiolanes and thioacetals.[15] We expected the radical to be reduced largely from the axial direction (**20.3** to **20.4**)[16] and, if the connecting chain c-b-a were suitably constituted, cleavage of the *O*-c bond would then liberate the required alcohol (**20.4** → **20.5**).

Accordingly, we converted 4-*t*-butylcyclohexanone into the oxathiolane derivatives **21.3**[17] (Scheme 21). However, refluxing **21.3** with Bu_3SnH and AIBN in PhH or PhMe gave an mixture of unidentified compounds, and so we examined a different derivative.



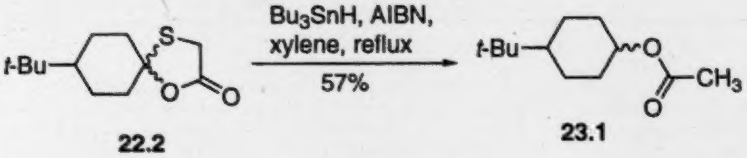
Scheme 21

Condensation between 4-*t*-butylcyclohexanone and mercaptoacetic acid **22.1** was catalyzed by TsOH, furnishing the oxathiolane derivative **22.2**[18] as a mixture of two isomers (Scheme 22).



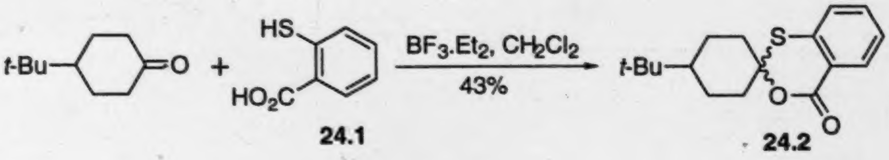
Scheme 22

We then tried to reduce **22.2** using Bu_3SnH and AIBN in different solvents. Refluxing **22.2** with Bu_3SnH and AIBN in PhH did not effect the reduction. When reduction was carried out in refluxing PhMe, the conversion was only 55%. We finally found that more than 6 equiv. of Bu_3SnH are needed for complete reduction of **22.2** in refluxing xylene and even then the yield was moderate (57%) (Scheme 23).



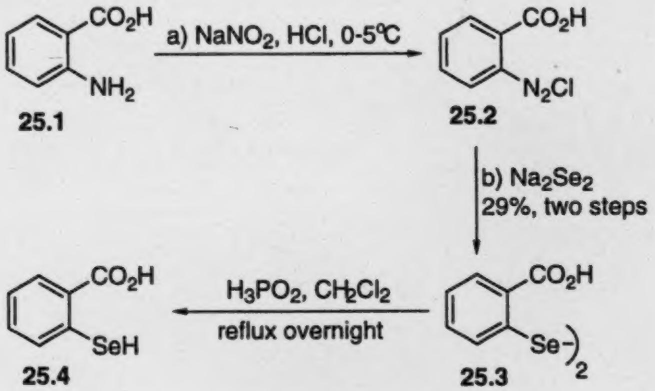
Scheme 23

Condensation between 4-*t*-butylcyclohexanone and thiosalicylic acid in the presence of $BF_3.OEt_2$ gave two separable isomers (**24.2**) in low yield (43%); refluxing **24.2** with Bu_3SnH and AIBN in PhMe gave a mixture of unidentified compounds (Scheme 24).



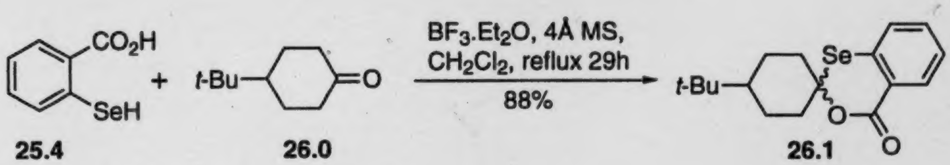
Scheme 24

These observations caused us to replace sulfur by selenium, and we decided that the selenium should be bound to an aromatic ring. Such a construct would avoid the probable necessity of two equivalents of stannane to reduce two carbon-selenium bonds, since PhSe remains intact under conditions where an alkyl-selenium bond is cleaved. The known 2-hydroselenobenzoic acid[19] **25.4** appeared to be suitable for our purposes (Scheme 25). We prepared it from the corresponding diselenide **25.3** which, in turn, was made by a slight modification of the literature procedure[20] (see Experimental section).



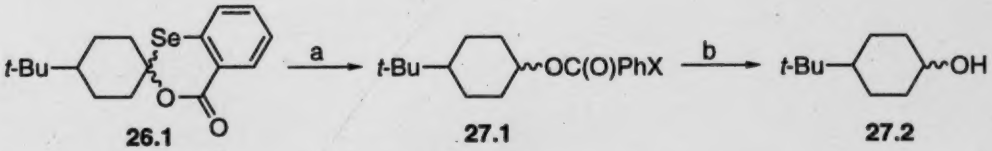
Scheme 25

Reduction to the 2-hydroselenobenzoic acid was most conveniently carried out with hypophosphorous acid just prior to use. The condensation of 2-hydroselenobenzoic acid **25.4** with ketones was tried under a variety of conditions. $LaCl_3$ did not effect condensation between 4-*t*-butylcyclohexanone and **25.4**. When $LaCl_3$ was replaced by $ZnCl_2$, only 10% of the desired lactone **26.1** (Scheme 26) was obtained. When the reaction was catalyzed by $BF_3.Et_2O$, but without the presence of 4 Å molecular sieves, an impure sample of **26.1** was obtained in 44% yield. We finally found that the condensation was best done in the presence of $BF_3.OEt_2$ and 4Å molecular sieves in refluxing CH_2Cl_2 (Scheme 26); under these conditions **26.1** was prepared in 88% yield.



Scheme 26

With **26.1** in hand, we sought to reduce it under radical conditions. Treatment of the **26.1** with Bu_3SnH, either thermally, in refluxing PhH in the presence of AIBN or at room temperature in the presence of Et_3B and air, served to



a. Bu_3SnH, initiator, PhH; b. MeOH, H_2O, K_2CO_3.

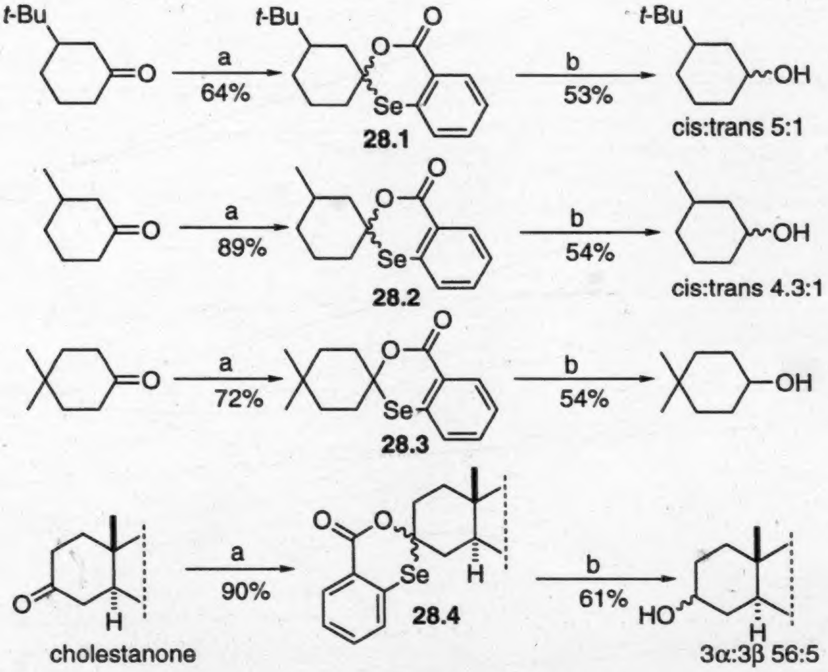
Initiator	Bu_3SnH equiv.	temp °C	time h	yield % of **27.2**	*trans:cis*
AIBN	3.7	80	11	46	not measured
Et_3B	2.15	25	36	67	16:1

Scheme 27

cleave the aliphatic carbon-selenium bond, and give what we presume to be a mixture of epimeric esters **27.1** (Scheme 27, X = unidentified selenium-tin species).

Treatment of crude **27.1** with a mild base (K_2CO_3, aqueous MeOH) served to liberated the corresponding alcohols **27.2**. Better results were obtained with Et_3B; the yield of alcohol **27.2** was then 67% with *trans*:*cis* ratio of 16:1.

Based on the optimized conditions found for 4-*t*-butylcyclohexanone, we examined four more examples, which are shown in Scheme 28.



a. ketones, $BF_3.Et_2O$, 4 Å MS, then 2-hydroselenobenzoic acid;
b. i. Bu_3SnH, Et_3B, PhH, rt; ii. K_2CO_3, MeOH, H_2O.

Scheme 28

Condensation of 3-*t*-butylcyclohexanone with 2-

hydroselenobenzoic acid in the presence of $BF_3.Et_2O$ and 4Å molecular sieves in refluxing CH_2Cl_2 gave lactone **28.1** as a mixture of two isomers in 64% yield. Reduction of **28.1** using Bu_3SnH and Et_3B, followed by hydrolysis of the resultant ester (K_2CO_3, MeOH, H_2O), furnished 3-*t*-butylcyclohexanol in 53% yield with a *cis*:*trans* ratio of 5:1 (^1H NMR).

Following the same procedure, 3-methylcyclohexanone was reduced to 3-methylcyclohexanol in 48% yield (3 steps) with a *cis*:*trans* ratio of 4.3:1 (both yield and isomer ratio were determined by glc).

4,4-Dimethylcyclohexanone was also reduced to 4,4-dimethylcyclohexanol in 39% yield overall (glc).

In the case of cholestanone, lactones **28.4** were obtained as two separable isomers in 90% yield. Reduction of **28.4**, followed by hydrolysis, gave cholestanols as two isomers in a combined yield of 61% and with a $3\alpha:3\beta$ ratio of 56:5.

In all cases the equatorial isomer was the major product to the extent of 4.3:1 to 16:1.

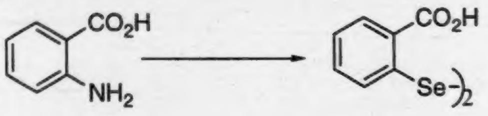
Conclusion

A new free radical method for the conversion of cyclohexanones into cyclohexanols has been developed. Reaction of cyclohexanones with 2-hydroselenobenzoic acid, stannane reduction and basic hydrolysis gives mainly equatorial cyclohexanols. The degree of selectivity is only modest, and the method involves three steps. It would seem that the procedure would be worth trying only in cases where conventional reagents did not afford the desired equatorial alcohol. As a general reduction method, it might be of interest to apply the sequence to aldehydes and acyclic ketones.

Experimental

Unless stated to the contrary, the general procedures used previously[21] in this laboratory were followed. The symbols s′, d′, t′, and q′ used for ^{13}C NMR signals indicate zero, one, two, or three attached hydrogens, respectively. Compounds were judged to be pure if they were homogeneous by TLC and gave high quality ^{1}H and ^{13}C NMR spectra free of impurity signals.

2,2′-Diselanediyldibenzoic acid (25.3).

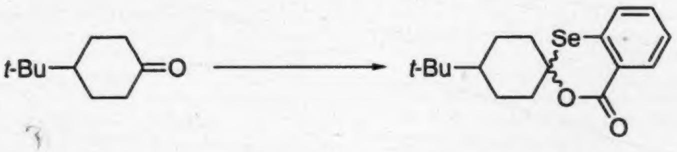


25.1 **25.3**

The literature procedure[20] was modified. A mixture of Se powder (16 g, 0.2 mmol) and KOH pellets (24 g, 0.43 mmol) was heated in a round-bottomed flask to 230-240 °C for 5-6 h (Ar atmosphere). The mixture was cooled and distilled water (250 mL) was added.

A solution of $NaNO_2$ (6.9 g, 0.1 mmol) in water (28 mL) was added dropwise over ca 30 min to a stirred and cooled (0-5 °C) solution of anthranilic acid (**25.1**) (13.7 g, 0.1 mmol) and concentrated hydrochloric acid (20 mL) in water (100 mL). The resulting solution was poured into a jacketed and cooled (ice-water) addition funnel and added dropwise over ca 1 h to the stirred and cooled (ice-salt bath) mixture obtained as described above from Se and KOH. Evolution of N_2 was observed and, when this had subsided, the mixture was heated up slowly (over ca 1 h) to reflux. Refluxing was then continued for 30 min, and the hot mixture was filtered. The filtrate was acidified to pH 2 (pH paper) by addition of concentrated hydrochloric acid. The gray precipitate was separated by filtration and mixed with AcOH (80 mL). The mixture was refluxed for 30 min, and filtered hot. The solid was added to AcOH (20 mL) and this mixture was again refluxed for 30 min and filtered hot. The resulting solid was added to dioxane (70 mL) and the mixture was refluxed for 20 min. Undissolved impurities were filtered off while the mixture was still hot, and the filtrate was evaporated to leave 2,2'-diselanediyldibenzoic acid (**25.3**) (5.65 g, 28%) as a brown solid: mp 304-306 °C (lit.[22] 296-297 °C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.35 (t, *J* = 9.1 Hz, 1 H), 7.47 (t, *J* = 9.1, 1 H), 7.67 (d, *J* = 9.1 Hz, 1 H), 8.06 (d, *J* = 9.1 Hz, 1 H).

4'-(1,1-Dimethylethyl)spiro[4*H*-3,1-benzoxaselenin-2,1'-cyclohexan]-4-one (26.1).

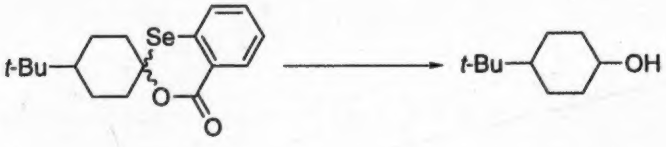


26.0 **26.1**

2,2′-Diselanediyldibenzoic acid (**25.3**) (479 mg, 1.20 mmol) was added to stirred H_3PO_2 (hypophosphorous acid) (50%, 8 mL) under Ar, and the mixture was refluxed overnight. The solution was cooled and extracted with degassed (by bubbling Ar) CH_2Cl_2 (40 mL). The organic layer was transferred by syringe to degassed brine (50 mL) contained in a 200-mL round-bottomed flask (protection from air). The mixture was shaken for 5 min, and the CH_2Cl_2 layer was removed by syringe, and dried ($MgSO_4$). The dried solution was transferred by syringe to a flask containing 4Å molecular sieves (Ar atmosphere).

4-(1,1-Dimethylethyl)cyclohexanone (**26.0**) (155 mg, 1.01 mmol), 4Å molecular sieves (150 mg), and then $BF_3.Et_2O$ (0.35 mL, 2.9 mmol) were added to a solution of degassed, dry CH_2Cl_2 (10 mL), and the mixture was stirred for 30 min at room temperature. A solution of 2-hydroselenobenzoic acid, prepared in the first part of this experiment, was then added at a fast dropwise rate by syringe. The mixture was refluxed for 29 h (Ar atmosphere), and the solvent was evaporated (water pump). Flash chromatography of the residue over silica gel (3.5 x 15 cm), using 100:1:1 hexane-Et_3N-EtOAc, gave **26.1** (301 mg, 88%) as an oil that was a mixture of two diastereoisomers: FTIR ($CHCl_3$ cast) 1717 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.54-0.86 (m, 9 H), 1.04-1.76 (m, 7 H), 2.14-2.36 (m, 1 H), 2.36-2.56 (m, 1 H), 6.78-6.99 (m, 2 H), 6.99-7.14 (m, 1 H), 8.26-8.44 (m, 1 H); ^{13}C NMR (C_6D_6, 100 MHz) 23.0 (t′); 24.5 (t′), 27.2 (q′), 27.4 (q′), 31.8 (s′), 32.1 (s′), 38.4 (t′), 39.3 (t′), 46.6 (d′), 46.8 (d′), 85.0 (s′), 89.8 (s′), 125.7 (s′), 126.4 (d′), 126.5 (s′), 126.6 (d′), 130.7 (d′), 130.8 (d′), 132.7 (d′), 132.8 (d′), 133.2 (d′), 133.4 (d′), 163.4 (s′), 163.6 (s′); exact mass *m/z* calcd for $C_{17}H_{22}O_2{}^{80}Se$ 338.07849, found 338.0778.

4-(1,1-Dimethylethyl)cyclohexanols (27.2).

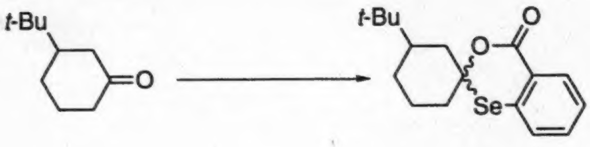


26.1 **27.2**

Compounds **26.1** (273 mg, 0.810 mmol), Bu_3SnH (0.56 mL, 2.1 mmol), and Et_3B (1 M in THF, 1.05 mL, 1.05 mmol) were added with stirring to dry PhH (15 mL) in an open round-bottomed flask. Stirring was continued for 84 h (^1H NMR control), by which point no further change in the ^1H NMR spectrum was observed. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 12 cm), using 1:20 EtOAc-hexane, gave an uncharacterized mixture (212 mg). MeOH (10 mL) was added to this material, followed by water (1 drop) and K_2CO_3 (266 mg, 1.93 mmol). The mixture was refluxed overnight, and then evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using CH_2Cl_2 and then CH_2Cl_2 containing increasing amounts of MeOH, up to 1:20 MeOH-CH_2Cl_2, gave *cis*-4-(1,1-

dimethylethyl)cyclohexanol (5 mg, 4%) and *trans*-4-(1,1-dimethylethyl)cyclohexanol (80.1 mg, 63%), each identified by spectral (^{1}H and ^{13}C NMR) comparison with data reported for a authentic samples.

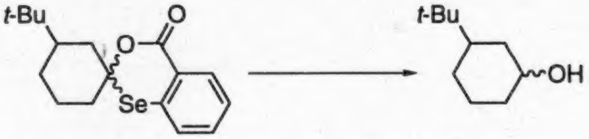
3′-(1,1-Dimethylethyl)spiro[4*H*-3,1-benzoxaselenin-2,1′-cyclohexan]-4-one (28.1).



28.1

The procedure used for **26.1** was followed with 2,2′-diselanediyldibenzoic acid (**25.3**) (488 mg, 1.22 mmol), H_3PO_2 (50%, 10 mL), CH_2Cl_2 (35 mL) and brine (45 mL) for the first step, and 3-(1,1-dimethylethyl)cyclohexanone (122 mg, 0.792 mmol), 4Å molecular sieves (200 mg), $BF_3.Et_2O$ (0.30 mL, 2.5 mmol), CH_2Cl_2 (13 mL), an initial reaction time of 45, and a reflux period of 76 h. Flash chromatography of the residue over silica gel (3 x 15 cm), using 100:1:1 hexane-Et_3N-EtOAc, gave **28.1** (170 mg, 64%) as an oil: FTIR (CH_2Cl_2 cast) 1716 cm^{-1}; ^{1}H NMR (C_6D_6, 360 MHz) δ 2.57-0.70 (m, 9 H), 2.16-2.36 (m, 2 H), 2.36-2.60 (m, 4 H), 2.16-2.72 (m, 2 H), 2.68-2.76 (m, 1 H), 6.74-6.88 (m, 2 H), 6.94-7.04 (m, 1 H), 8.26-8.40 (m, 1 H); ^{13}C NMR (C_6D_6, 75 MHz) δ 22.4 (t′), 23.8 (t′), 26.1 (t′), 26.3 (t′), 27.1 (q′), 27.3 (q′), 32.0 (s′), 38.2 (t′), 39.0 (t'), 40.3 (t'), 40.6 (t'), 42.8 (d'), 45.6 (d'), 86.6 (s'), 90.9 (s'), 125.9 (s'), 126.6 (d'), 126.8 (d'), 130.7 (d'), 130.8 (d'), 130.9 (d'), 133.0 (d'), 133.3 (d'), 133.6 (d'), 163.6 (s'), 163.7 (s'); exact mass *m/z* calcd for $C_{17}H_{22}O_2{}^{80}Se$ 338.07849, found 338.0785.

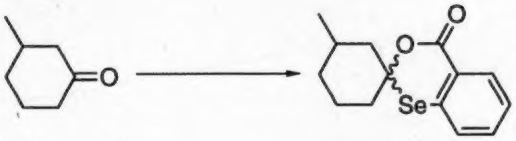
3-(1,1-Dimethylethyl)cyclohexanols.



28.1

Compounds **28.1** (122 mg, 0.362 mmol), Bu_3SnH (0.35 mL, 1.30 mmol), and Et_3B (1 M in THF, 0.45 mL, 0.45 mmol) were added with stirring to dry PhH (7 mL) in an open round-bottomed flask. Stirring was continued for 72 h (^1H NMR control), by which point no further change in the ^1H NMR spectrum was observed. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 11 cm), using 1:20 EtOAc-hexane, gave an uncharacterized mixture (87 mg). MeOH (3.5 mL) was added to this material, followed by water (1 drop) and K_2CO_3 (135 mg, 0.98 mmol). The mixture was refluxed overnight, and then extracted with Et_2O. The organic extract was washed with brine, dried ($MgSO_4$), and evaporated to afford a 5:1 *cis/trans* mixture of 3-(1,1-dimethylethyl)cyclohexanols (30 mg, 53%) as an oil. The material was identified by comparison of its ^{1}H NMR spectrum with published data.[23]

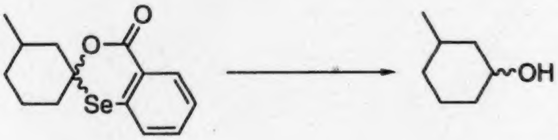
3′-Methylspiro[4*H*-3,1-benzoxaselenin-2,1′-cyclohexan]-4-one (28.2).



28.2

The procedure used for **26.1** was followed with 2,2′-diselanediyldibenzoic acid (**25.3**) (505 mg, 1.26 mmol), H_3PO_2 (50%, 9 mL), CH_2Cl_2 (40 mL) and brine (50 mL) for the first step, and 3-methylcyclohexanone (0.14 mL, 1.1 mmol), 4Å molecular sieves (200 mg), $BF_3.Et_2O$ (0.40 mL, 3.3 mmol), CH_2Cl_2 (10 mL), an initial reaction time of 40 min, and an overnight reflux period. Flash chromatography of the residue over silica gel (3.5 x 13 cm), using 100:1:1 hexane-Et_3N-EtOAc, gave **28.2** (290 mg, 89%) as an oil that was a mixture of two diastereoisomers: FTIR ($CHCl_3$ cast) 1716 cm^{-1}; ^{1}H NMR (C_6D_6, 360 MHz) δ 0.54-0.66 (m, 3 H), 1.16-1.66 (m, 5 H), 1.70-2.06 (m, 2 H), 2.14-2.32 (m, 2 H), 6.86-6.94 (m, 2 H), 7.07 (d, *J* = 10.9 Hz, 1 H), 8.36 (d, *J* = 10.9 Hz, 1 H); ^{13}C NMR (C_6D_6, 100 MHz) δ 21.34 (q′), 21.63 (q′), 21.74 (t′), 23.21 (t′), 27.95 (d′), 30.04 (d′), 33.39 (t′), 33.49 (t′), 37.78 (t′), 38.36 (t′), 46.45 (t′), 46.90 (t′), 85.51 (s′), 89.38 (s'), 125.59 (s'), 126.34 (s'), 126.42 (d'), 126.56 (d'), 130.63 (d'), 130.69 (d'), 132.75 (d'), 132.84 (d'), 133.20 (d'), 133.40 (d'), 163.39 (s'), 163.44 (s'); exact mass *m/z* calcd for $C_{14}H_{16}O_2{}^{80}Se$ 296.03156, found 296.0317.

3-Methylcyclohexanols.

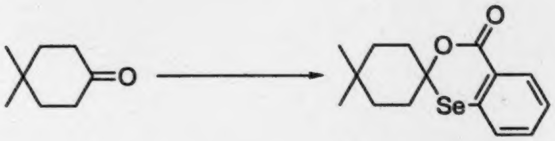


28.2

Compounds **28.2** (290 mg, 0.980 mmol), Bu_3SnH (0.58 mL, 2.2 mmol), and Et_3B (1 M in THF, 1.05 mL, 1.05 mmol) were added with stirring to dry PhH (10 mL) in an open round-bottomed flask. Stirring was continued for 96 h (^1H NMR and tlc control, silica, 1:10 EtOAc-hexane), by which point no further change was observed. Evaporation of the solvent and flash chromatography over silica gel (3.5 x 8 cm), using 1:100 EtOAc-hexane, gave an uncharacterized mixture (320 mg). MeOH (18 mL) was added to this material, followed by water (1 drop) and Na_2CO_3 (650 mg, 6.20 mmol). The mixture was refluxed overnight, and then concentrated to a small volume. The residue was extracted continuously with Et_2O for 1 day. Evaporation of most of the solvent gave a crude mixture of 3-methylcyclohexanols. The ^1H NMR spectrum showed that the ratio of *cis* and *trans* isomers was ca 1:4.34. 5-Nonanone

(40.2 mg) was then added to the crude alcohol as a standard and the yield (54%) was determined by glc (10% Carbowax 20 M, 90 °C). An authentic sample of the product was mixed with 5-nonanone for generating a calibration graph.

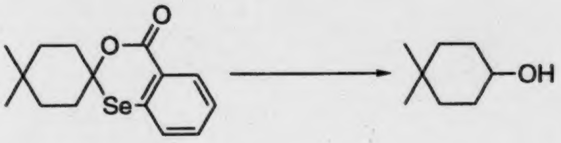
4′,4′-Dimethylspiro[4*H*-3,1-benzoxaselenin-2,1′-cyclohexan]-4-one (28.3).



28.3

The procedure used for **26.1** was followed with 2,2′-diselanediyldibenzoic acid (**25.3**) (4.49 g, 1.22 mmol), H_3PO_2 (50%, 9 mL), CH_2Cl_2 (30 mL) and brine (40 mL) for the first step, and 4,4-dimethylethylcyclohexanone (150 mg, 1.19 mmol), 4Å molecular sieves (200 mg), $BF_3.Et_2O$ (0.36 mL, 2.9 mmol), CH_2Cl_2 (15 mL), an initial reaction time of 1 h, and a reflux period of 76 h. Flash chromatography of the residue over silica gel (3 x 15 cm), using 100:1:1 hexane-Et_3N-EtOAc, gave **28.3** (270 mg, 72%) as an oil: FTIR (PhMe cast) 1717 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 0.57-0.73 (m, 6 H), 1.03-1.21 (m, 2 H), 1.21-1.39 (m, 2 H), 1.79-2.13 (m, 4 H), 6.73-6.85 (m, 2 H), 6.94 (d, *J* = 9.1 Hz, 1 H), 8.34 (d, *J* = 9.1 Hz, 1 H); ^{13}C NMR (C_6D_6, 75 MHz) δ 27.3 (q′), 27.8 (q′), 28.0 (q′), 29.2 (s′), 34.9 (t′), 35.4 (t′), 87.8 (s′), 126.5 (s′), 126.7 (d′), 130.6 (d'), 132.8 (d'), 132.9 (s'), 133.2 (d'), 163.5 (s'); exact mass *m/z* calcd for $C_{15}H_{18}O_2{}^{80}Se$ 310.04721, found 310.0468.

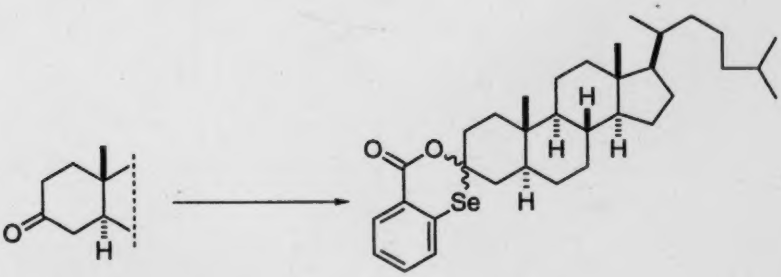
4,4-Dimethylethylcyclohexanol.



28.3

Compound **28.3** (264 mg, 0.854 mmol), Bu_3SnH (0.74 mL, 2.8 mmol), and Et_3B (1 M in THF, 1.15 mL, 1.15 mmol) were added with stirring to dry PhH (10 mL) in an open round-bottomed flask. Stirring was continued for 96 h (^1H NMR control), by which point no further change was observed. Evaporation of the solvent and flash chromatography over silica gel (3 x 15 cm), using 1:20 EtOAc-hexane, gave an uncharacterized mixture (210 mg). MeOH (5 mL) was added to this material, followed by water (1 drop) and Na_2CO_3 (250 mg, 1.81 mmol). The mixture was refluxed overnight, diluted with Et_2O (50 mL), and washed with brine (2 x 30 mL). Most of the solvent was evaporated and the product was identified by comparison of the ^1H NMR spectrum of the resulting oil with that of an authentic sample. 5-Nonanone (64.4 mg) was then added to the crude alcohol as a standard and the yield (54%) was determined by glc (10% Carbowax 20 M, 90 °C). An authentic sample of the product was mixed with 5-nonanone for generating a calibration graph.

Spiro[4*H*-3,1-benzoxaselenin-2,3′-cholestan]-4-one (28.4).

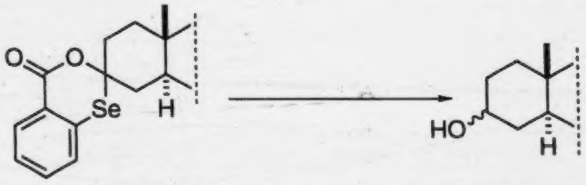


cholestanone **28.4**

The procedure used for **26.1** was followed with 2,2′-diselanediyldibenzoic acid (**25.3**) (683 mg, 1.70 mmol), H_3PO_2 (50%, 11 mL), CH_2Cl_2 (50 mL) and brine (50 mL) for the first step, and 5α-cholestanone (463 mg, 1.20 mmol), 4Å molecular sieves (200 mg), $BF_3.Et_2O$ (0.46 mL, 3.8 mmol), CH_2Cl_2 (10 mL), an initial reaction time of 30 min, and a reflux period of 84 h. Flash chromatography of the residue over silica gel (3.5 x 12 cm), using 100:1:1 hexane-Et_3N-EtOAc, gave **28.4**, which was obtained as three fractions: isomer #1 (277 mg, 41%), fraction #2, which was a mixture of both isomers (76 mg, 11%), and isomer #2 (259 mg, 38%), each as oils: Isomer #1 had: FTIR ($CHCl_3$ cast) 1717 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.52-1.44 (m, 28 H), 1.44-1.66 (m, 10 H), 1.66-2.06 (m, 6 H), 2.14-2.26 (m, 1 H), 2.36-2.46 (m, 1 H), 6.80-6.94 (m, 2 H), 7.09 (d, *J* = 6.3 Hz, 1 H), 8.40 (d, *J* = 6.3 Hz, 1 H); ^{13}C NMR (C_6D_6, 100 MHz) δ 11.2 (q'), 12.0 (q'), 18.8 (q'), 20.9 (t'), 22.5 (q'), 22.8 (q'), 24.2 (t'), 27.8 (t'), 28.1 (d'), 28.4 (t'), 31.5 (t'), 34.2 (t'), 35.2 (s' or t'), 35.3 (d'), 35.4 (s' or t'), 36.0 (d'), 36.4 (t'), 39.7 (t'), 39.8 (t'), 40.9 (d'), 41.7 (t'), 42.6 (s'), 53.1 (d'), 56.0 (d'), 56.5 (d'), 85.4 (s'), 125.8 (s'), 126.4 (d'), 130.6 (d'), 132.9 (d'), 133.2 (s'), 133.3 (d'), 163.5 (s'); exact mass *m/z* calcd for $C_{34}H_{50}O_2{}^{80}Se$ 570.29761, found 570.2964.

Isomer #2 had: FTIR ($CHCl_3$ cast) 1719 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 0.64-1.66 (m, 39 H), 1.78-2.08 (m, 6 H), 2.14-2.24 (m, 1 H), 6.86-6.94 (m, 2 H), 7.06-7.12 (m, 1 H), 8.38-8.46 (m, 1 H); ^{13}C NMR (C_6D_6, 100 MHz) δ 11.96 (q'), 12.0 (q'), 18.8 (q'), 21.2 (t'), 22.5 (q'), 22.8 (q'), 24.1 (t'), 27.7 (t'), 28.1 (d'), 28.3 (t'), 31.8 (t'), 34.56 (t'), 35.2 (d'), 35.85 (s' or t'), 35.89 (s' or t'), 35.94 (d'), 36.4 (s' or t'), 39.7 (t'), 40.0 (t'), 41.0 (t'), 42.6 (s'), 43.7 (d'), 53.9 (d'), 56.2 (d'), 56.5 (d'), 90.0 (s'), 126.4 (s'), 126.5 (d'), 130.7 (d'), 130.8 (d'), 132.8 (s'), 133.1 (d'), 163.5 (s'); exact mass *m/z* calcd for $C_{34}H_{50}O_2{}^{80}Se$ 570.29761, found 570.2978.

5α-Cholestan-3-ols.



28.4

Compound **28.4** (isomer #1, 270 mg, 0.475 mmol), Bu_3SnH (0.30 mL, 1.1 mmol), and Et_3B (1 M in THF, 0.53 mL, 0.53 mmol) were added with stirring to dry PhH (10 mL) in an open round-bottomed flask. Stirring was continued for 90 h (^1H NMR and tlc control, silica, 1:10 EtOAc-hexane), by which point no further change in the ^1H NMR spectrum was observed. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 10 cm), using 1:20 EtOAc-hexane, gave an uncharacterized mixture (213 mg). MeOH (15 mL) was added to this material, followed by water (1 drop) and K_2CO_3 (134 mg, 0.97 mmol). The mixture was refluxed overnight, and then evaporated. Flash chromatography of the residue over silica gel (3.5 x 16 cm), using 100:1 CH_2Cl_2-MeOH, gave 5α-cholestan-3α-ol (10 mg, 5%) and 5α-cholestan-3β-ol (102 mg, 56%), each identified by spectral comparison (^1H and ^{13}C NMR) with data reported for authentic samples.

A single repetition of the experiment, using isomer #2, gave 5α-cholestan-3α-ol (2.4%) and 5α-cholestan-3β-ol (24%).

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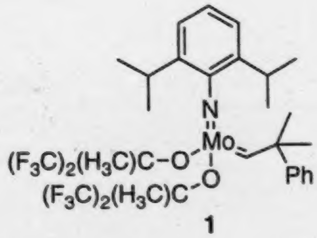
Chapter 2

Tandem ring-closing metathesis–radical cyclization based on 4-(phenylseleno)butanal and methyl 3-(phenylseleno)propanoate – a route to bicyclic compounds

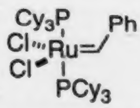
Introduction

The construction of rings represents a central theme in natural product synthesis.[1] Among the various available methods, transition metal catalyzed ring-closing olefin metathesis (RCM) has been become a very powerful tool in recent years.[2]

Four typical catalysts for RCM are the Shrock molybdenum-based catalyst **1** and Grubbs' ruthenium-based catalysts **2**, **3** and **4**.



1



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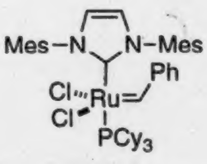

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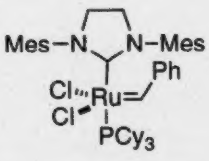

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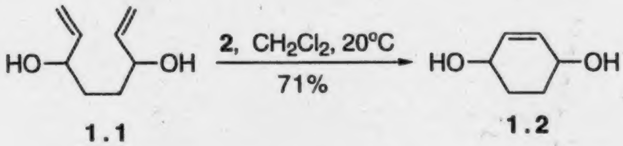
Catalyst **1** was the first of these catalyst to become widely used. The most impressive feature of **1** is its high activity, which allows it to react with both terminal and internal olefins. However, this catalyst is limited by the high oxophilicity of the metal center, which renders it extremely sensitive to oxygen and moisture. Consequently, the synthesis and handling of **1** is difficult and its applications are limited by its moderate to poor functional group tolerance.

By contrast, catalyst **2** is air stable for a reasonable period in the solid form. Although **2** is less active than **1**, its high functional group tolerance makes **2** ideal for a wide range of synthetic organic applications.

The second generation of Grubbs' catalysts, **3** and **4**, rival the activity of **1** and retain the functional group tolerance of **2**. Especially, they can perform the RCM of sterically demanding dienes to from tri- and tetrasubstituted olefins. Here, I will discuss RCM briefly.

1. Synthesis of monocyclic systems

Treatment of bisolefin diols such as **1.1** with **2** at room



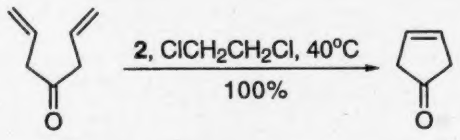
1.1

1.2

Scheme 1

temperature gave the diol **1.2** in 71% yield (Scheme 1).[3]

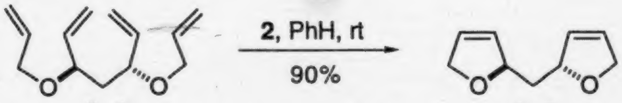
Catalyst **2** is also compatible with ketones, as shown in Scheme 2.[4]



2.1 **2.2**

Scheme 2

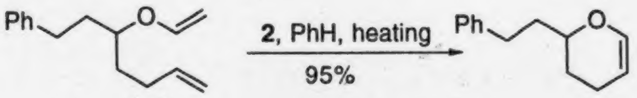
RCM of allylic ether **3.1** using **2** provided bicyclic ether **3.2** in high yield (Scheme 3).[5]



3.1 **3.2**

Scheme 3

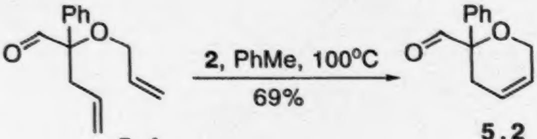
Enol ether **4.1** reacted with **2**, furnishing dihydropyran **4.2** in 95% (Scheme 4).[6]



4.1 **4.2**

Scheme 4

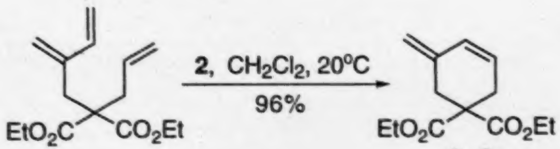
RCM of bisolefin aldehyde **5.1** yielded aldehyde **5.2** in 69% yield (Scheme 5).[7]



5.1 **5.2**

Scheme 5

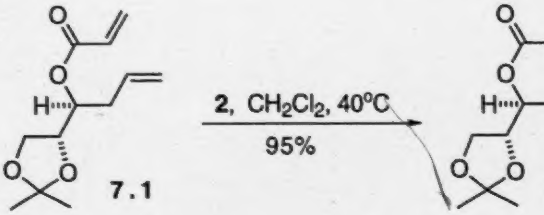
Catalyst **2** reacted preferentially with the two less substituted double bonds of diester **6.1** to give cyclohexene **6.2** in high yield (Scheme 6).[8]



6.2

Scheme 6

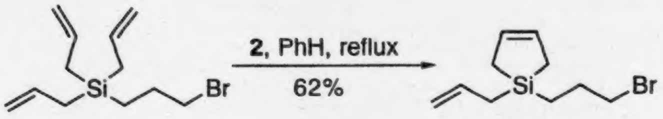
Acrylate **7.1**, when treated with **2**, afforded unsaturated lactone **7.2** in 95% yield (Scheme 7).[9] The high yield of this reaction demonstrated that the acetal functionality in **7.1** did not interfere with the reactivity of **2**.



7.1 **7.2**

Scheme 7

RCM of bromosilane **8.1** gave rise to silacycle **8.2** in moderate yield (Scheme 8).[10]

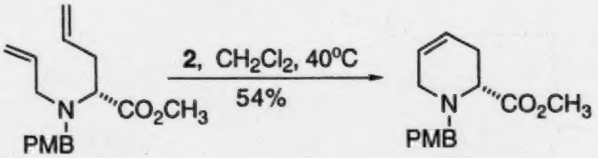


8.1

8.2

Scheme 8

Compounds possessing basic or nucleophilic nitrogen suppress the activity of the catalysts. Such substrates, as a rule, must be deactivated by conversion to amides, carbamates, imides and sulfonamides or by protonation. For example, tertiary amine **9.1** when reacted with **2**, providing piperidine **9.2** in only 54% yield (Scheme 9).[11]



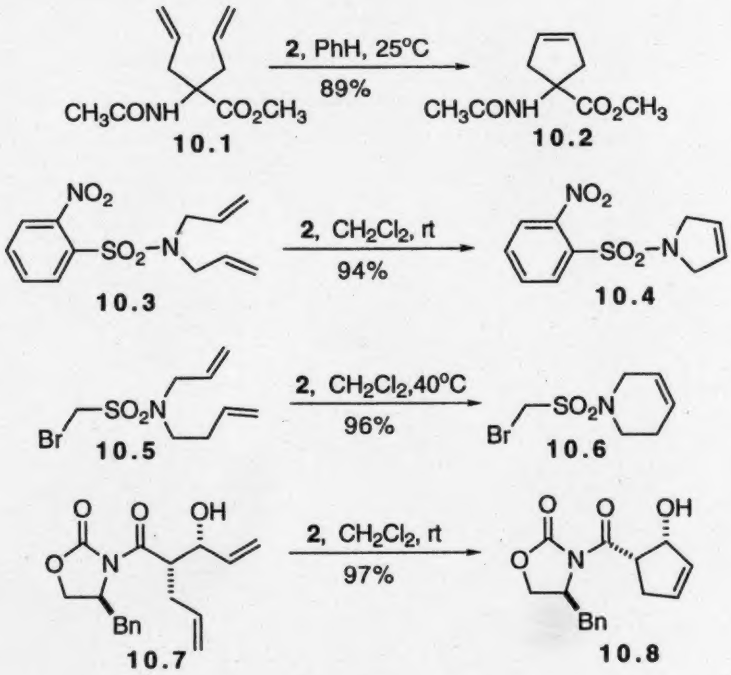
9.1

9.2

Scheme 9

On the contrary, RCM of amides,[12] sulfonamides[13] and imides[14] afforded ring-closing products in higher yields, and some examples are shown in Scheme 10.

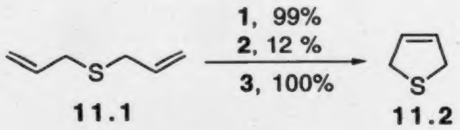
In general, catalyst **1** appears to be much less tolerant of functionality in the substrate than catalyst **2**. However, there are exceptions to this generalization, particularly when the functional group contains 'soft' electron pairs (as present in sulfides) which apparently coordinate to ruthenium in **2** better than to molybdenum in **1**. This surprising observation has been attributed to the greater steric



Scheme 10

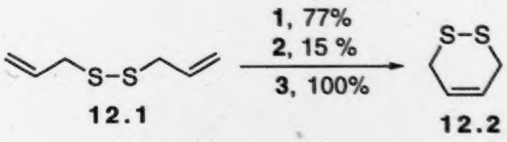
hindrance around the molybdenum atom. Catalysts **3** and **4** also have higher tolerance of sulfur than **2** because they have sterically hindered *N*-heterocyclic carbenes attached to ruthenium.

RCM of sulfide **11.1**, when catalyzed by **1**, **2** and **3**, gave dihydrothiophene **11.2** in yield of 99%, 12% and 100% respectively (Scheme 11).[15]



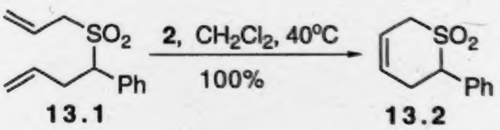
Scheme 11

Allylic disulfide (**12.1**) when treated with 5 mol% of **3** in refluxing CD_2Cl_2 for 4 h, gave quantitatively dihydrodithiine **12.2**. Under similar conditions **2** led to 15% yield of **12.2**. Shrock's catalyst **1**, used in 10 mol% for 1 h in PhH at 20 °C, afforded the dithiine **12.2** in 77% yield (Scheme 12).[15]



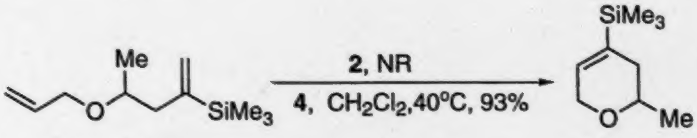
Scheme 12

The fact that allylic sulfone **13.1** gave quantitatively dihydrothiopyran **13.2** by performing the RCM with catalyst **2** in CH_2Cl_2 indicates that the sulfone group does not coordinate with ruthenium (Scheme 13).[16]



Scheme 13

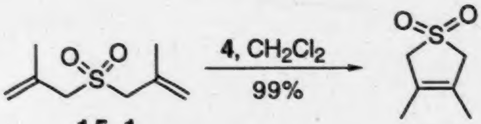
Usually catalyst **2** is good enough to effect RCM to give trisubstituted olefins when the substituent on the double bond is not bulky group (i.e. Me-, $HOCH_2$-, isopropyl).[8,17] The desired compounds are obtained in moderate to high yields. But, when the substituent on the double bond is bulky (i.e. Ph-, Me_3Si-, etc.), catalyst **4** works much better. For example, while catalyst **2** failed to cyclize trimethylsilyl substituted olefin **14.1**, **14.2** was made in the presence of 3 mol% of **4** in near quantitative yield (Scheme 14).[18]



14.1 **14.2**

Scheme 14

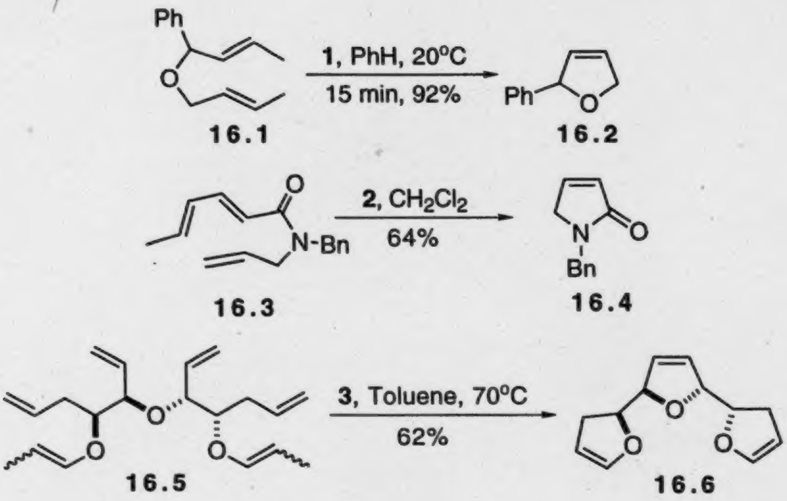
Catalyst **4** is also an efficient catalyst for synthesis of tetrasubstituted olefins by the RCM process. One example is shown in Scheme 15.[16]



15.1 **15.2**

Scheme 15

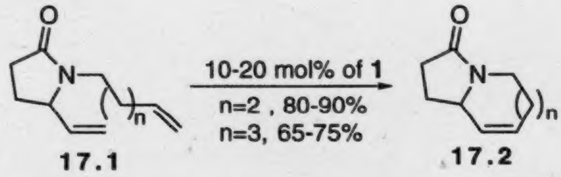
Scheme 16 shows some internal olefins that undergo RCM to give cycloalkenes.[19]



Scheme 16

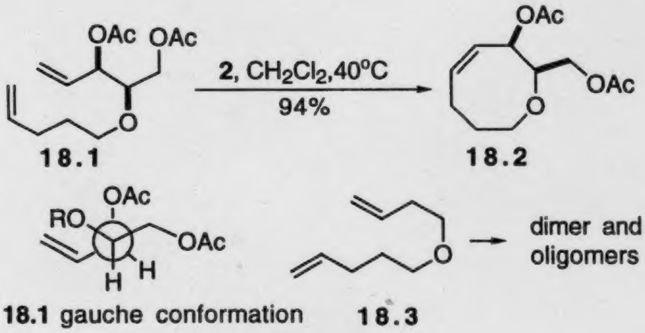
2. Medium and large ring closure

Because of enthalpic (increasing strain in the transition state) and entropic influences (probability of the chain ends meeting), medium-sized rings are the most difficult to prepare. In order to facilitate RCM reactions to give the desired medium-sized ring, usually a ring is installed to limit the conformational freedom of the chain. For example, seven- and eight-membered ring can be annulated onto a γ-lactam (Scheme 17).[20]



Scheme 17

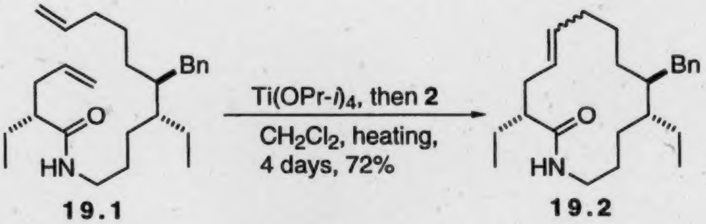
Appropriately positioning substituents on the chain carrying the two olefinic groups can also facilitate the macrocyclization. Crimmins reported on the use of the gauche effect of 1,2-dioxygen substituents to facilitate ring closure (Scheme 18).[21]



Scheme 18

Many examples of large ring closures by RCM have been reported. So far, twelve-,[22a] thirteen-,[22b] fourteen-,[22c] fifteen-,[22d] sixteen-,[22e] eighteen-,[22f] nineteen-,[22g] twenty-,[22h] twenty-one-,[22i] and twenty-two-membered rings[22f] have been made.

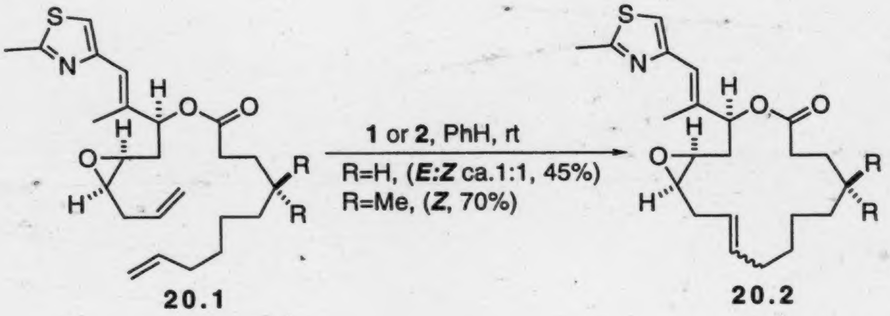
In synthesis of 6-norfluvirucinin B_1, fourteen-membered lactam **19.2** was formed in 72% yield as a mixture of *trans* and



Scheme 19

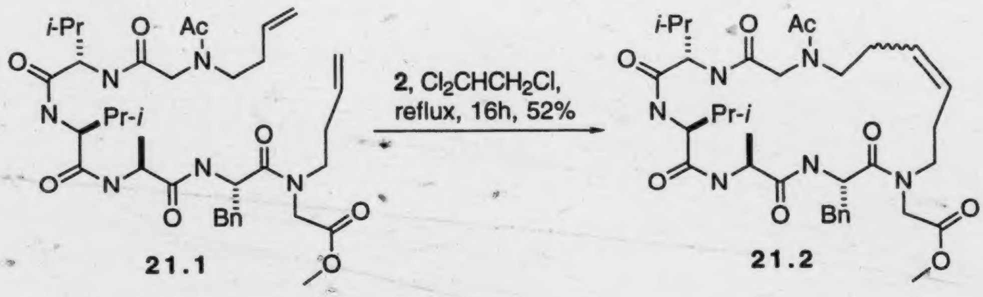
cis isomers after heating with catalyst **2** in CH_2Cl_2 for 4 days (Scheme 19).[22c]

In Danishefsky's approach towards epothilone A, RCM provided the sixteen-membered lactone **20.2** (Scheme 20).[23] Catalysts **1** and **2** gave substantially identical results. Evidently, the catalysts are compatible with the heterocycle and the epoxide.



Scheme 20

The Liskamp group made a variety of cyclic peptides employing RCM reactions.[22g] The largest ring was a twenty-two-membered peptide, which is shown in Scheme 21.



Scheme 21

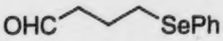
Conclusion

As the above examples show, RCM is an immensely powerful method for making rings, and the procedure can be used for a wide range of ring sizes and compound classes. The importance of the subject in synthetic chemistry is already well-established, and will undoubtedly increase.

Results and Discussion

The usefulness of radical cyclization is often determined by the ease with which the cyclization substrates can be made. In this regard, the nature of the homolyzable group is, of course, important, because this determines the stages at which it may be introduced; in particular, early introduction can avoid the extra steps involved in replacing a non-homolyzable group by one that is homolyzable.

For radical generation, phenyl selenides have the distinct advantage that the PhSe group is usually inert to basic or nucleophilic reagents[24] and, among the common transformations, usually care need be exercised only in the choice of oxidizing agent[25,26] when selenium is present. We have found that the PhSe group is compatible with the Grubbs catalyst $(Cy_3P)_2Cl_2Ru{=}CHPh$ **2**,[27,30,31] and we report that α,ω-(phenylseleno) carbonyl compounds, such as 4-(phenylseleno)-butanal (**5**[32]) and methyl 3-(phenylseleno)propanoate (**6**[33]) are

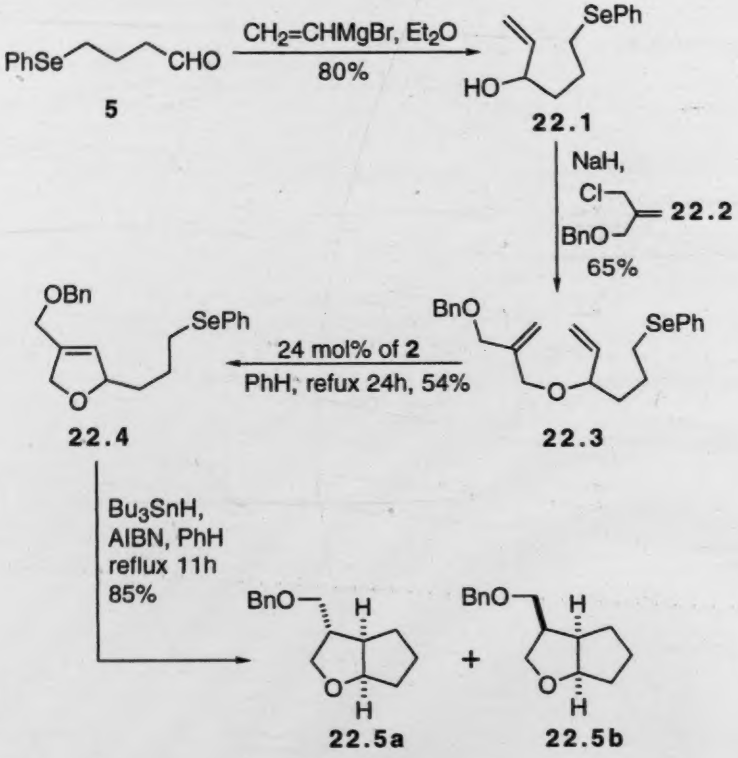


5

6

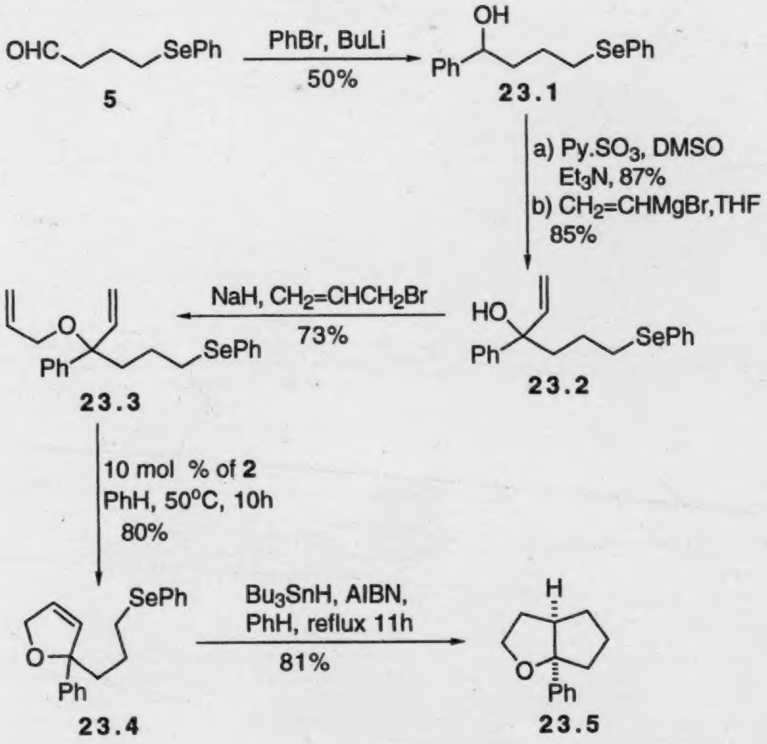
useful for the construction of substances that undergo sequential ring-closing metathesis[34] and radical cyclization. The PhSe group allows the use of anionic chemistry that would not be suitable in the presence of halogen or carboxyl groups as the eventual source of radicals.[35] Several publications have reported that the catalyst is usually not compatible with *sulfide* substrates.[27,28]

Coupling of **5** with vinylmagnesium bromide gave allylic alcohol **22.1** in 80% yield (Scheme 22). This was treated subsequently with NaH and the allylic chloride **22.2**,[36] affording 65% of bisolefin **22.3**. The RCM reaction was carried out by refluxing a mixture of **22.3** and catalyst **2** in PhH for 24 h, furnishing dihydrofuran **22.4** in 54% yield. Slow addition of a PhH solution of Bu_3SnH and AIBN into a refluxing PhH solution of **22.4** provided the reduced cyclopentafurans **22.5a** and **22.5b** in 85% yield (**22.5a**:**22.5b** = 1:2.4).



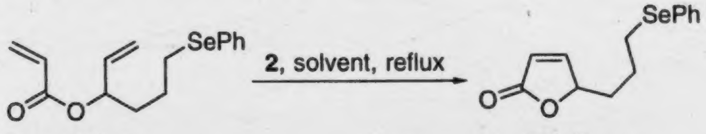
Scheme 22

Aldehyde **5** was also converted into bisolefin **23.3** in 4 steps using conventional methods with an overall yield of 32% (Scheme 23). Reaction of **23.3** with **2** in PhH gave dihyrofuran **23.4** in 80% yield. Radical cyclization also went smoothly, furnishing the desired bicyclic ether **23.5** in high yield (81%).



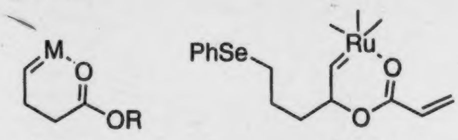
Scheme 23

Acrylate **24.1** (Scheme 24) was prepared from **22.1** with acryloyl chloride (Et_3N, DMAP, CH_2Cl_2) in 64% yield. However, RCM of **24.1** turned out to be troublesome in the beginning. After refluxing a mixture of **24.1** and **2** in CH_2Cl_2 for ca 36 h, conversion was 74%, and the yield was 61% (based on conversion). Switching to higher boiling point solvents (PhH, PhMe) did not improve either the conversion or the yield of the reaction.



24.1 **24.2**

1. CH_2Cl_2, 74% conversion, 46% yield, 61% based on conversion;
2. PhH, 69% conversion, 40% yield, 58% based on conversion;
3. PhMe, 60% conversion, 33% yield, 55% based on conversion;
4. CH_2Cl_2, 0.43 eqiv. Ti(OPr-*i*)$_4$, 94% conversion, 61%, 65% based on conversion

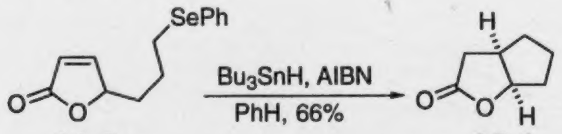


24.3 **24.4**

Scheme 24

A literature search then led us to Fürstner's report about the formation of unproductive stable six-membered chelates (cf. **24.3**) resulting from coordination of the metal with the ester carbonyl in attempted RCM.[22b,37] Accordingly, we assumed that in RCM of **24.1**, it was also possible that the ruthenium may chelate with the carbonyl oxygen, and the formation of this stable metal complex stopped the reaction. Fürstner has also shown that the presence of Ti(OPr-*i*)$_4$ destabilizes such unproductive complexes and results in effective cyclization. Acting on Fürstner's discovery, we tried RCM of **24.1** in the presence of Ti(OPr-*i*)$_4$. To our satisfaction, the conversion of the reaction was 94% and the yield was 65%, based on conversion.

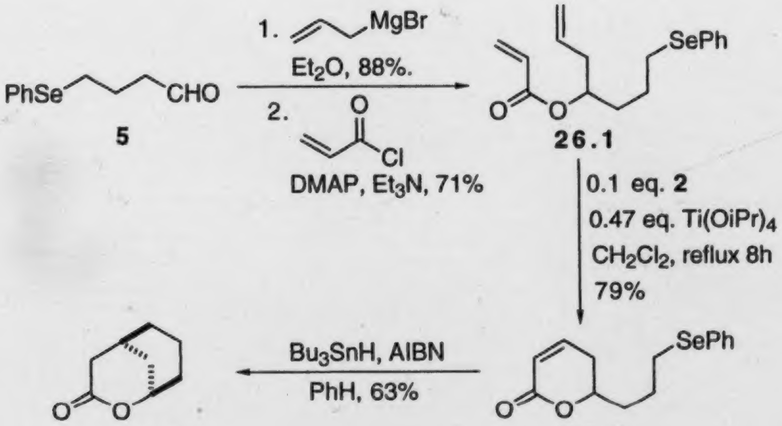
The radical cyclization of **24.2** under standard condition went smoothly, giving the desired bicyclic lactone **25.1** in 66% yield (Scheme 25).



24.2 **25.1**

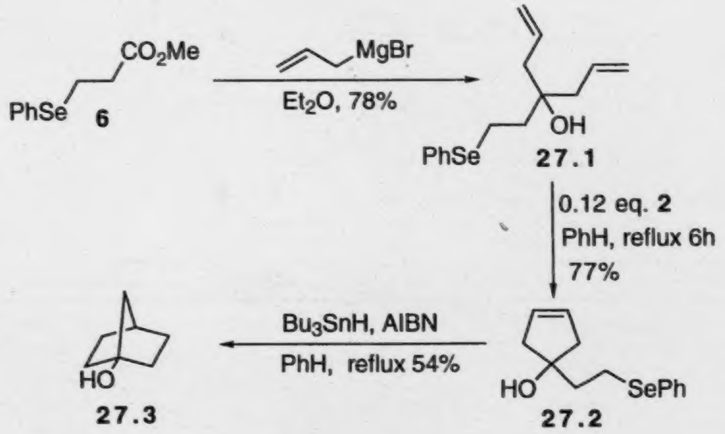
Scheme 25

Similarly, acrylate **26.1** was made from **5** in two steps (Scheme 26). RCM of **26.1** in the presence of Ti(OPr-*i*)$_4$ afforded lactone **26.2** in 79% yield, and radical cyclization under standard conditions provided bicyclic lactone **26.3** (63%).



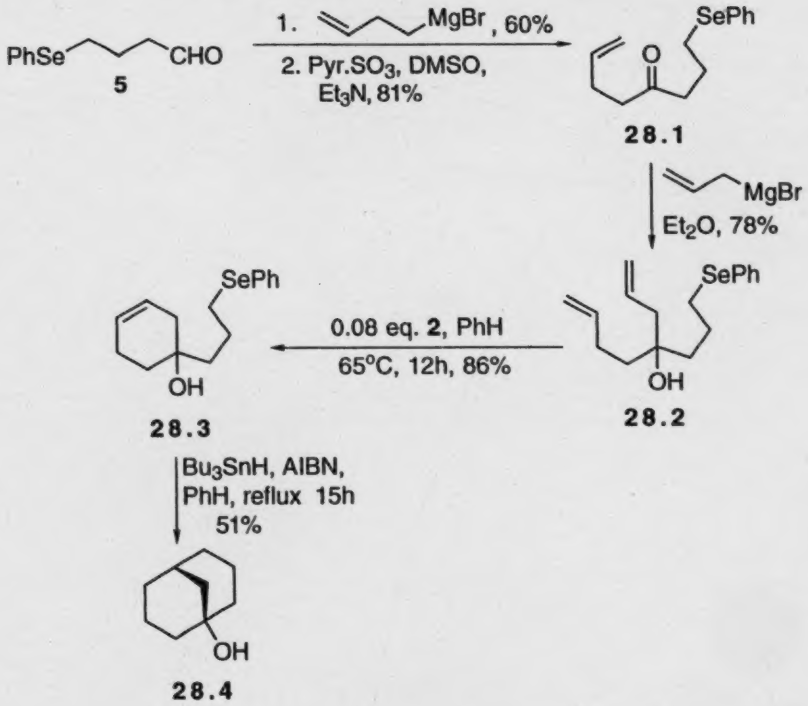
Scheme 26

Ester **6** was converted into bisolefin **27.1** by the action of allylmagnesium bromide (Scheme 27). RCM of **27.1** with 0.12 equiv. of **2** in refluxing PhH[38] gave alcohol **27.2**, which was cyclized to bicyclic alcohol **27.3** in 54% yield. The RCM reaction was very slow in refluxing CH_2Cl_2.[38]



Scheme 27

Bisolefin **28.2** was prepared from **5** using conventional methods in 3 steps with a total yield of 40% (Scheme 28). RCM of **28.2** with 0.08 equiv. of **2** in PhH gave alcohol **28.3** in high yield (86%), and radical cyclization of **28.3** provided bicyclic alcohol **28.4**[39] in 51% yield.



Scheme 28

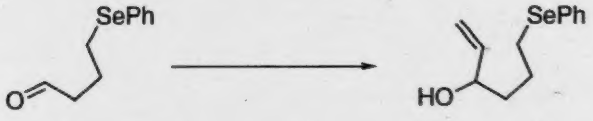
Conclusion

We have found out the phenylseleno group is compatible with Grubbs' catalyst **2**. Sequential application of ring-closing metathesis and radical cyclization provides a new powerful method for synthesis of bicyclic compounds. Bicyclic ethers, lactones and alcohols have been prepared by this method. The advantage of the present procedure is that the phenylseleno group can be introduced at an early stage, and before ring closing metathesis. In conventional methodology, a protected oxygen would normally be used before the metathesis step and then the oxygen function would be deprotected and replaced by a homolyzable group. These additional steps can now be avoided by the finding that the phenylseleno group is tolerated by the Grubbs catalyst. No further work on this methodology is planned, but the possibility of using the method for natural product synthesis will undoubtedly be kept in mind by chemists in this laboratory.

Experimental

The same general procedures as used previously[40] in this laboratory were followed. The symbols s', d', t', and q' used for ^{13}C NMR signals indicate zero, one, two, or three attached hydrogens, respectively. Compounds were judged to be pure if they were homogeneous by TLC and gave high quality ^{1}H and ^{13}C NMR spectra free of impurity signals.

6-(Phenylseleno)-1-hexen-3-ol (22.1).

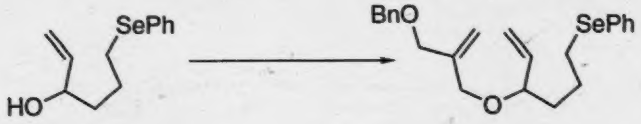


5 **22.1**

Vinylmagnesium bromide (1 M in THF, 5.0 mL) was added to a stirred and cooled (0 °C) solution of aldehyde **5**[32] (550 mg, 2.42 mmol) in Et_2O (10.5 mL). Stirring was continued overnight, the cold bath being left in place, but not recharged. The mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with Et_2O (2 x 35 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 11 cm), using 5:100 to 10:100 EtOAc-hexane mixtures, gave alcohol **22.1** (490 mg, 80%) as oil: FTIR ($CHCl_3$ cast) 3381 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.62-1.87 (m, 5 H), 2.94 (t, J = 6.8 Hz, 2 H), 4.06-4.13 (m, 1 H), 5.07-5.26 (m, 2 H), 5.78-5.90 (m, 1 H), 7.18-7.30 (m, 3

H), 7.45-7.53 (m, 2 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz) δ 26.0 (t′), 27.8 (t′), 36.9 (t′), 72.6 (d′), 114.9 (t′), 126.8 (d′), 129.0 (d′), 130.4 (s′), 132.5 (d′), 140.9 (d′); exact mass *m/z* calcd for $C_{12}H_{16}O^{80}Se$ 256.03662, found 256.0366.

4-Oxa-2-[(phenylmethoxy)methyl]-5-[3-(phenylseleno)propyl]-1,6-heptadiene (22.3).

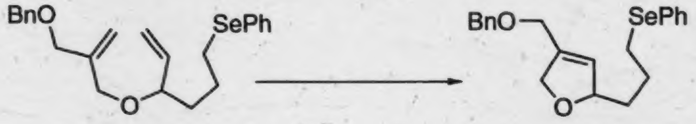


22.1 **22.3**

NaH (60% in mineral oil, 65 mg, 1.6 mmol) was added to a stirred solution of alcohol **22.1** (300 mg, 1.18 mmol) in THF (20 mL). After 30 min, NaI (15 mg), 2-chloromethyl-3-[(phenylmethyl)oxy]-1-propene[36] (252 mg, 128 mmol) in THF (7 mL) were added, and the stirred mixture was refluxed overnight. Evaporation of the solvent, and flash chromatography of the residue over silica gel (12 x 3 cm), using 1:50 EtOAc-hexane, gave ether **22.3** (320 mg, 65%) as an oil: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.58-1.92 (m, 4 H), 2.88-2.97 (m, 2 H), 3.66-3.75 (m, 1 H), 3.90 (d, *J* = 14.5 Hz, m, 1 H), 4.05-4.14 (m, 3 H), 4.54 (s, 2 H), 5.14-5.26 (m, 4 H), 5.66-5.74 (m, 1 H), 7.24-7.40 (m, 8 H), 7.47-7.56 (m, 2 H); ^{13}C NMR (CDCl$_3$, 100.6 MHz) δ 26.1 (t′), 27.9 (t′), 35.5 (t′), 68.9 (t′), 71.1 (t′), 72.2 (t′), 80.2 (d′), 114.0 (t′), 117.3 (t′), 126.7 (d′), 127.6 (d′), 127.7 (d′), 128.4 (d′), 129.0

(d′), 130.6 (s′), 132.6 (d′), 138.4 (s′), 138.7 (d′), 143.1 (s′); exact mass *m/z* calcd for $C_{23}H_{28}O_2{}^{80}Se$ 416.12546, found 416.1255.

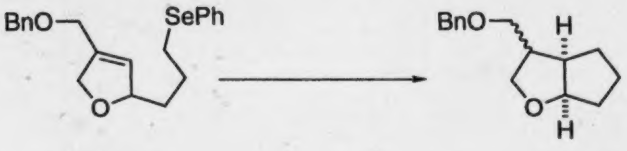
4-[(Phenylmethoxy)methyl]-2-[3-(phenylseleno)-propyl]-2,5-dihydrofuran (22.4).



22.3 **22.4**

$(Cy_3P)_2Cl_2Ru{=}CHPh$ (19.3 mg, 0.0235 mmol) was added to a stirred solution of ether **22.3** (115 mg, 0.277 mmol) in dry PhH (2 mL), and stirring was continued overnight at 50 °C. A further portion of the catalyst (38.8 mg, 0.0471 mmol) was added, and the solution was refluxed for 24 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 13 cm), using 1:100 to 10:100 EtOAc-hexane mixtures, gave **22.4** (58 mg, 54%) as an oil: ^1H NMR ($CDCl_3$, 360 MHz) δ 1.56-1.88 (m, 4 H), 2.95 (t, *J* = 8.2 Hz, 2 H), 4.12 (s, 2 H), 4.54 (s, 2 H), 4.55-4.66 (m, 2 H), 4.84-4.92 (m, 1 H), 5.66 (br s, 1 H), 7.19-4.42 (m, 8 H), 7.47-7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 26.0 (t′), 28.0 (t′), 36.0 (t′), 65.6 (t′), 72.4 (t′), 75.2 (t′), 85.9 (d′), 126.0 (d′), 126.7 (d′), 127.7 (d′), 127.8 (d′), 128.5 (d′), 129.0 (d′), 130.5 (d′), 132.6 (s′), 138.0 (s′), 138.2 (s′); exact mass *m/z* calcd for $C_{21}H_{24}O_2{}^{80}Se$ 388.09415, found 388.0921.

(3α,3aα,6aα)-3-[(Phenylmethoxy)methyl]-hexahydro-2*H*-cyclopenta[*b*]furan (22.5a) and (3α,3aβ,6aβ)-3-[(Phenylmethoxy)methyl]hexahydro-2*H*-cyclopenta[*b*]furan (22.5b).



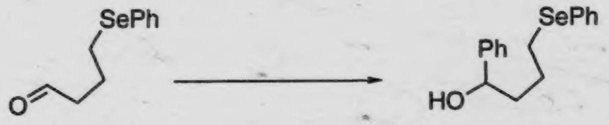
22.4 **22.5a,b**

A solution of Bu_3SnH (124 μL, 0.461 mmol) and AIBN (17.7 mg, 0.108 mmol) in PhH (10.5 mL) was added over 10.5 h by syringe pump to a refluxing solution of ether **22.4** (115 mg, 0.297 mmol) in PhH (25 mL). After the addition, refluxing was continued for an arbitrary period of 30 min. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 13.5), using 1:200 to 10:200 EtOAc-hexane mixtures, gave **22.5a** and **22.5b** as a separable mixture of two isomers, **22.5a** (less polar, 17.1 mg, 25%) and **22.5b** (more polar, 41.1 mg, 60%). Isomer **22.5a** had: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.47-1.87 (m, 6 H), 2.13-2.22 (m, 1 H), 2.29-2.38 (m, 1 H), 3.37-3.58 (m, 3 H), 3.96-4.04 (m, 1 H), 4.38-4.47 (m, 1 H), 4.53 (s, 2 H), 7.24-7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 24.2 (t′), 32.5 (t′), 34.2 (t′), 46.3 (d′), 48.1 (d′), 71.5 (t′), 72.0 (t′), 73.2 (t′), 84.9 (d′), 127.596 (d′), 127.627 (d'), 128.4 (d'), 138.4 (s'); exact mass *m/z* calcd for $C_{15}H_{20}O_2$ 232.14633, found 232.1466.

Isomer **22.5b** had: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.44-1.86 (m, 6 H), 2.58-2.74 (m, 2 H), 3.42-3.63 (m, 3 H), 3.86-3.94 (m, 1 H), 4.48-4.55 (m, 3 H), 7.27-7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 25.5 (t'), 26.1 (t'), 34.0 (t'), 42.9 (d'), 45.3 (d'), 69.5 (t'), 70.7 (t'), 73.2 (t'), 86.2 (d'), 127.6 (d'), 128.4 (d'), 138.3 (s'); exact mass *m/z* calcd for $C_{15}H_{20}O_2$ 232.14633, found 232.1458.

TROESY measurements showed that the less polar isomer has the $BnOCH_2$ group *syn* to the adjacent ring fusion hydrogen, there being an NOE between these protons.

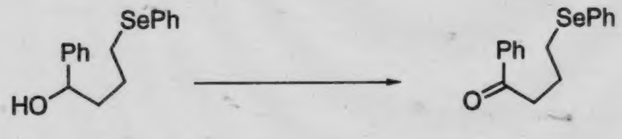
1-Phenyl-3-(phenylseleno)butan-1-ol (23.1).



BuLi (2.5 M in hexanes, 0.50 mL, 1.3 mmol) was added to a stirred and cooled (-76 °C) solution of PhBr (217 mg, 1.38 mmol) in THF (10 mL). The resulting solution was stirred for 70 min and then transferred by cannula into a stirred and cooled (0 °C) solution of aldehyde **5** (275 mg, 1.21 mmol) in THF (12 mL). After 4.5 h at 0 °C, the THF was evaporated and, aqueous NH_4Cl (20 mL) was added to the residue. The mixture was extracted with Et_2O (2 x 35 mL), and the combined organic extract were washed with brine (30 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 9 cm), using 1:200 EtOAc-hexane, gave alcohol **23.1** (185 mg, 50%) as an oil: FTIR ($CHCl_3$ cast) 3388 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 1.62-2.02 (m, 5 H), 2.83-2.98 (m, 2 H), 4.60-4.72 (m, 1 H), 7.17-7.54 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 26.4 (t′), 27.8 (t′), 28.2 (t′), 74.0 (d′), 125.9 (d′), 126.8 (d′), 127.6 (d′), 128.5 (d′), 129.1 (d′), 130.4 (s′), 132.6 (d′), 144.5 (s′); exact mass *m/z* calcd for $C_{16}H_{18}O^{80}Se$: 306.05228, found 306.0526.

3-Phenyl-6-(phenylseleno)-1-hexen-3-ol (23.2).

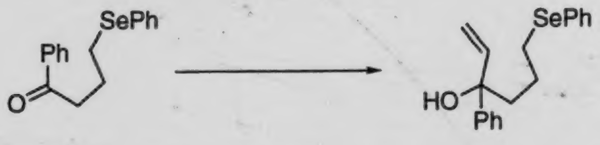
(a) 1-Phenyl-3-(phenylseleno)butan-1-one.



23.1 -

Pyridine-SO_3 complex (178 mg, 1.12 mmol) in DMSO (1.2 mL) was added over 5 min to a stirred and cooled (water bath at 20 °C) solution of alcohol **23.1** (115 mg, 0.378 mmol) and Et_3N (0.52 mL, 3.7 mmol) in DMSO (1.1 mL).[25] After the addition, the solution was stirred for 4 h, and then adjusted to pH 3 by addition of 10% hydrochloric acid. The mixture was extracted with Et_2O (2 x 25 mL), and the combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 8 cm), using 2:100 to 7:100 EtOAc-hexane mixtures, gave 1-phenyl-3-(phenylseleno)butan-1-one (100 mg, 87%) as an oil: FTIR ($CHCl_3$ cast) 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.96-2.17 (m, 2 H); 2.93 (t, J = 7.3 Hz, 2 H), 3.03 (t, J = 6.8 Hz, 2 H), 7.08-7.25 (m, 3 H), 7.28-7.53 (m, 5 H), 7.78-7.93 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 24.4 (t′), 27.4 (t′), 38.0 (t′), 126.9 (d′), 128.0 (d′), 128.6 (d′), 129.1 (d′), 130.0 (s′), 132.6 (d′), 133.0 (d′), 136.9 (s′), 199.4 (s′); exact mass *m/z* calcd for $C_{16}H_{16}O^{80}Se$ 304.03662, found 304.0371.

(b) 3-Phenyl-6-(phenylseleno)-1-hexen-3-ol (23.2).

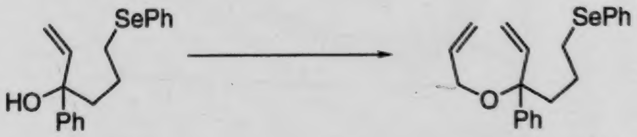


- **23.2**

Vinylmagnesium bromide (1 M in THF, 2.8 mL, 2.8 mmol) was added to a stirred and cooled (0 °C) solution of the ketone made in the previous step (610 mg, 2.01 mmol) in THF (15 mL). Stirring was continued overnight, the cold bath being left in place, but not recharged. The mixture was quenched with saturated aqueous NH_4Cl (30 mL), and extracted with Et_2O (2 x 45 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 9

cam), using 1:20 EtOAc-hexane, gave tertiary alcohol **23.2** (565 mg, 85%) as an oil: FTIR ($CHCl_3$ cast) 3457 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.58-2.17 (m, 6 H), 2.92 (t, *J* = 7.3 Hz, 2 H), 5.18 (d, *J* = 10.9 Hz, 1 H), 5.32 (d, *J* = 15.5 Hz, 1 H), 6.13-6.27 (m, 1 H), 7.22-7.31 (m, 4 H), 7.32-7.40 (m, 1 H), 7.42-7.52 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.2 (t′), 28.4 (t′), 41.8 (t′), 76.8 (s′), 112.8 (t′), 125.4 (d′), 126.7 (d′), 126.9 (d′), 128.3 (d′), 129.0 (d′), 130.4 (s′), 132.6 (d′), 144.1 (d′), 145.3 (s′); exact mass *m/z* calcd for $C_{18}H_{20}O^{80}Se$ 332.06793, found 332.0682.

4-Oxa-3-phenyl-3-[3-(phenylseleno)propyl]-1,6-heptadiene (23.3).

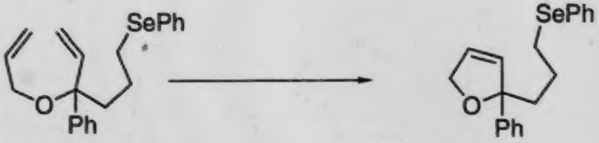


23.2 **23.3**

A solution of alcohol **23.2** (465 mg, 1.4 mmol) in THF (12 mL) was added to a stirred slurry of NaH (60% in mineral oil, 74 mg, 1.9 mmol) in THF (6 mL). After 5 h, allyl bromide (0.20 mL, 2.4 mmol) was added, and the mixture was refluxed overnight, cooled, and quenched with water (30 mL). The mixture was extracted with Et_2O (2 x 40 mL), and the combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue

over silica gel (2.5 x 12 cm), using 1:20 EtOAc-hexane, gave ether **23.3** (379 mg, 73%) as an oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.54-1.84 (m, 2 H), 2.06-2.24 (m, 2 H), 2.89 (t, J = 7.3 Hz, 2 H), 3.74-3.86 (m, 2 H), 5.14-5.19 (m, 1 H), 5.29-5.42 (m, 3 H), 5.87-6.04 (m, 2 H), 7.18-7.52 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.7 (t′), 28.5 (t′), 36.8 (t′), 63.7 (t′), 81.2 (s′), 115.2 (t′), 115.5 (t′), 126.6 (d′), 126.7 (d′), 127.0 (d′), 128.1 (d′), 129.0 (d′), 130.5 (s′), 132.6 (d′), 135.4 (d′), 141.7 (d′), 143.3 (s′); exact ms m/z calcd for $C_{21}H_{24}O^{80}S$ 372.09924, found 372.0991.

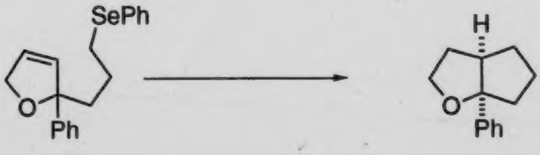
2-Phenyl-2-[3-(phenylseleno)propyl]-2,5-dihydrofuran (23.4).



23.3 **23.4**

$(Cy_3P)_2Cl_2Ru{=}CHPh$ (47.3 mg, 0.0574 mmol) was added to a stirred solution of ether **23.3** (211 mg, 0.569 mmol) in dry PhH (36 mL), and the solution was stirred overnight at 50 °C. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 11 cm), using 1:200 EtOAc-hexane, gave ether **23.4** (156 mg, 80%) as an oil: ^1H NMR ($CDCl_3$, 360 MHz) δ 1.71-1.86 (m, 2 H), 2.00-2.14 (m, 2 H), 2.92 (t, J = 7.1 Hz, 2 H), 4.66-4.81 (m, 2 H); 5.86-6.02 (m, 2 H), 7.16-7.54 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 24.8 (t′), 28.3 (t′), 41.4 (t′), 75.2 (t′), 93.3 (s′), 124.7 (d′), 125.9 (d′), 126.66 (d′), 126.71 (d′), 128.3 (d′), 129.0 (d′), 130.6 (s′), 132.44 (d′), 132.53 (d′), 145.7 (s′); exact mass *m/z* calcd for $C_{19}H_{20}O^{80}Se$ 344.06793, found 344.0689.

Cis-Hexahydro-6-phenyl-2*H*-cyclopenta[*b*]furan (23.5).

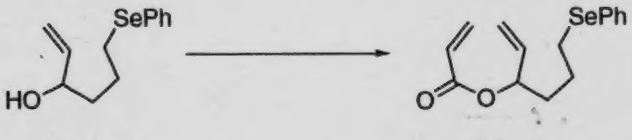


23.4 **23.5**

A solution of Bu_3SnH (0.15 mL, 0.56 mmol) and AIBN (13.6 mg, 0.083 mmol) in PhH (10 mL) was added over 10 h by syringe pump to a refluxing solution of ether **23.4** (94.0 mg, 0.274 mmol) in PhH (36 mL). After the addition, refluxing was continued for an arbitrary period of 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 10 cm), using 1:100 EtOAc-hexane, gave ether **23.5** (42 mg, 81%) as an oil: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.61-2.22 (m, 8 H); 2.69-2.80 (m, 1 H); 3.70 (q, J = 8.0, 1 H), 3.94-4.06 (m, 1 H), 7.16-7.46 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 25.4 (t′), 34.4 (t′), 34.8 (t′), 44.0 (t′), 51.3 (d′), 67.8 (t′), 76.7 (s′), 124.9 (d′), 126.2 (d′), 128.1 (d′), 147.3 (s′); exact mass *m/z* calcd for $C_{13}H_{16}O$ 188.12012, found

188.1198.

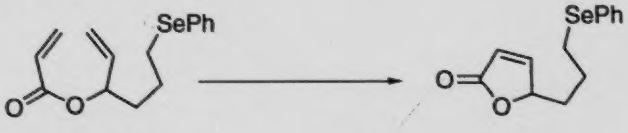
6-(Phenylseleno)-1-hexen-3-yl Propenoate (24.1).



22.1 **24.1**

Acryloyl chloride (0.30 mL, 3.7 mmol) was added over 2 min by syringe to a stirred and cooled (0 °C) solution of alcohol **22.1** (491 mg, 1.93 mmol), DMAP (36 mg, 0.30 mmol), and Et_3N (0.80 mL, 5.8 mmol) in CH_2Cl_2 (8 mL). Stirring at 0 °C was continued for 1 h, and the mixture was then quenched with saturated aqueous $NaHCO_3$ (2 mL), and extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with brine (35 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 12 cm), using 5:100 to 10:100 EtOAc-hexane mixtures, gave acryloate **24.1** (380 mg, 64%) as an oil: FTIR ($CHCl_3$ cast) 1723 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.67-1.88 (m, 4 H), 2.85-3.00 (m, 2 H), 5.12-5.38 (m, 3 H), 5.72-5.87 (m, 2 H), 6.04-6.18 (m, 1 H), 6.40 (d, *J* = 15.1 Hz, 1 H), 7.17-7.31 (m, 3 H), 7.42-7.53 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.6 (t′), 27.5 (t′), 34.1 (t′), 74.1 (d′), 116.9 (t′), 126.9 (d′), 128.6 (d′), 129.0 (d′), 130.1 (s′), 130.7 (t′), 132.7 (d′), 136.1 (d′), 165.4 (s′); exact mass *m/z* calcd for $C_{15}H_{18}O_2{}^{80}Se$ 310.04721, found 310.0472.

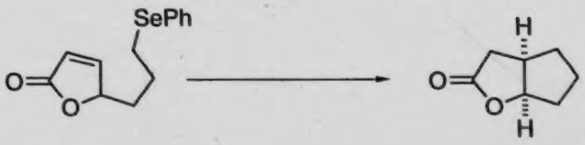
5-[3-(Phenylseleno)propyl]-5*H*-furan-2-one (24.2).



24.1 **24.2**

Ti(OPr-*i*)$_4$ (70 µL, 0.24 mmol) was added to a stirred solution of acryloate **24.1** (170 mg, 0.55 mmol) in dry CH_2Cl_2 (45 mL). The mixture was refluxed for 80 min,[22b,37] and then $(Cy_3P)_2Cl_2Ru{=}CHPh$ (45 mg, 0.055 mmol) in dry CH_2Cl_2 (10 mL) was added. Refluxing was continued and, after 30 h, another portion of Grubbs' catalyst (54 mg, 0.065 mmol) in CH_2Cl_2 (14 mL) was added. Refluxing was continued overnight, and the solvent was then evaporated. Flash chromatography of the residue over silica gel (3 x 10 cm), using 5:100 to 30:100 EtOAc-hexane mixtures, gave starting material **24.1** (10 mg) and lactone **24.2** (94 mg, 61% or 65% after correction for recovered starting material) as an oil: FTIR ($CHCl_3$ cast) 1751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.68-2.04 (m, 4 H), 2.95 (t, J = 5.9 Hz, 2 H), 4.97-5.08 (m, 1 H), 6.07-6.14 (m, 1 H), 7.23-7.35 (m, 3 H), 7.36-7.44 (m, 1 H), 7.45-7.56 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 25.6 (t'), 27.3 (t'), 32.9 (t'), 82.7 (t'), 121.8 (d'), 127.1 (d'), 129.2 (d'), 129.7 (s'), 132.9 (d'), 155.9 (d'), 172.9 (s'); exact mass m/z calcd for $C_{13}H_{14}O_2{}^{80}Se$ 282.01590, found 282.0163.

Cis-Hexahydrocyclopenta[*b*]furan-2-one (25.1).

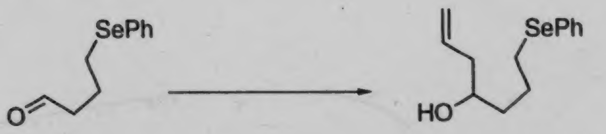


24.2 **25.1**

A solution of Bu_3SnH (120 μL, 0.446 mmol) and AIBN (11 mg, 0.065 mmol) in PhH (10.5 mL) was added over 10.5 h by syringe pump to a refluxing solution of lactone **24.2** (78.1 mg, 0.278 mmol) in PhH (20 mL). After the addition, refluxing was continued for an arbitrary period of 30 min. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 10 cm), using 5:100 to 20:100 EtOAc-hexane mixtures, gave bicyclic lactone **25.1**[41] (23 mg, 66%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48-1.93 (m, 5 H), 1.95-2.12 (m, 1 H), 2.30 (d, J = 15.8 Hz, 1 H), 2.75-2.94 (m, 2 H), 4.93-5.06 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 23.4 (t′), 33.5 (t′), 33.6 (t′), 36.0 (t′), 37.9 (d′), 86.4 (d′), 177.8 (s′).

7-(Phenylseleno)-1-hepten-4-yl Propenoate (26.1).

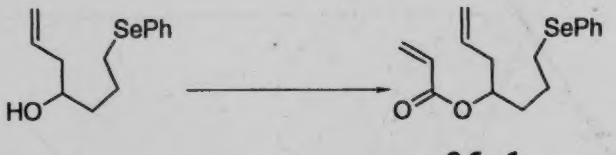
(a) 7-(Phenylseleno)-1-hepten-4-ol.



5 **-**

Allylmagnesium bromide (1 M in Et_2O, 1.3 mL, 1.3 mmol) was added to a stirred and cooled (0 °C) solution of aldehyde **5** (202 mg, 0.886 mmol) in dry Et_2O (10 mL). Stirring was continued overnight, the cold bath being left in place, but not recharged. The mixture was quenched with saturated aqueous NH_4Cl (10 mL), and extracted with Et_2O (2 x 25 mL). The combined organic extracts was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 9 cm), using 1:10 EtOAc-hexane, gave 7-(phenylseleno)-1-hepten-4-ol (209 mg, 87%) as an oil: FTIR ($CHCl_3$ cast) 3404 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.47-1.68 (m, 2 H), 1.69-1.94 (m, 3 H), 2.06-2.20 (m, 1 H), 2.21-2.33 (m, 1 H), 2.92 (d, J = 7.1 Hz, 2 H), 3.56-3.68 (m, 1 H), 5.06-5.16 (m, 2 H), 5.72-5.86 (m, 1 H), 7.16-7.32 (m, 3 H), 7.42-7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 26.3 (t′), 27.8 (t′), 36.7 (t′), 42.0 (t′), 70.1 (d′), 118.2 (t′), 126.7 (d′), 129.0 (d′), 130.4 (s′), 132.5 (d′), 134.6 (d′); exact mass *m/z* calcd for $C_{13}H_{18}O^{80}Se$ 270.05228, found 270.0522.

(b) 7-(Phenylseleno)-1-hepten-4-yl Propenoate (26.1).



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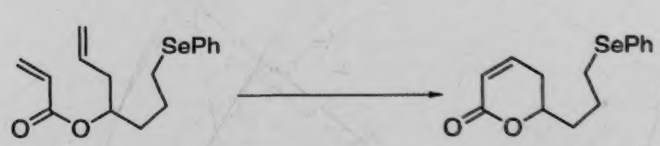
26.1

Acryloyl chloride (0.13 mL, 1.6 mmol) was added over 2 min by syringe to a stirred and cooled (0 °C) solution of 7-(phenylseleno)-1-hepten-4-ol made in the previous step (186 mg, 0.691 mmol), DMAP (15.6 mg, 0.128 mmol), and Et_3N (0.35 mL, 2.5 mmol) in CH_2Cl_2 (9 mL). Stirring at 0 °C was continued for 2 h, and the mixture was then quenched with saturated aqueous $NaHCO_3$ (10 mL), and extracted with Et_2O (2 x 35 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 10 cm), using 1:20 EtOAc-hexane, gave ester **26.1** (158 mg, 71%) as an oil: FTIR ($CHCl_3$ cast) 1721 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.66-1.82 (m, 4 H), 2.29-2.38 (m, 2 H), 2.84-2.96 (m, 2 H), 4.95-5.14 (m, 3 H), 5.66-5.84 (m, 2 H), 6.02-6.16 (m, 1 H), 6.38 (d, J = 15.3 Hz, 1 H), 7.19-7.30 (m, 3 H), 7.46-7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 25.8 (t′), 27.5 (t′), 33.5 (t′), 38.6 (t′), 72.8 (d′), 117.9 (t′), 126.8 (d′), 128.7 (d′), 129.1 (d′), 130.1 (s′), 130.5 (t′), 132.7 (d′), 133.3 (d′), 165.8 (s′); exact mass *m/z* calcd for $C_{16}H_{20}O_2{}^{80}Se$ 324.06284, found 324.0632.

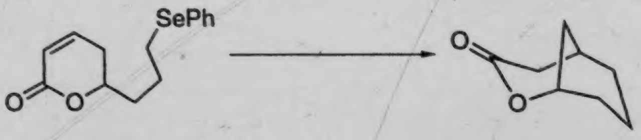
6-[3-(Phenylseleno)propyl]-5,6-dihydro-2*H*-pyran-2-one (26.2).



26.1 **26.2**

$Ti(OPr\text{-}i)_4$ (90 μL, 0.30 mmol) was added to a stirred solution of acryloate **26.1** (205 mg, 0.633 mmol) in dry CH_2Cl_2 (46 mL). The mixture was refluxed for 70 min,[22b,37] and then $(Cy_3P)_2Cl_2Ru{=}CHPh$ (49.2 mg, 0.0598 mmol) in dry CH_2Cl_2 (9 mL) was added. Refluxing was continued and, after 8 h, the solvent was evaporated. Flash chromatography of the residue over silica gel (3 x 10 cm), using 5:100 to 30:100 EtOAc-hexane, gave lactone **26.2** (148 mg, 79%) as an oil: FTIR ($CHCl_3$ cast) 1717 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.84-2.01 (m, 4 H), 2.23-2.34 (m, 2 H); 2.87-3.00 (m, 2 H), 4.34-4.45 (m, 1 H), 5.94-6.06 (m, 1 H), 6.78-6.88 (m, 1 H), 7.16-7.32 (m, 3 H), 7.39-7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 25.4 (t′), 27.4 (t′), 29.4 (t′), 34.7 (t′), 77.3 (d′), 121.4 (d′), 127.0 (d′), 129.1 (d′), 130.0 (s′), 132.7 (d′), 144.9 (d′), 164.3 (s′); exact mass *m/z* calcd for $C_{14}H_{16}O_2{}^{80}Se$ 296.03156, found 296.0321.

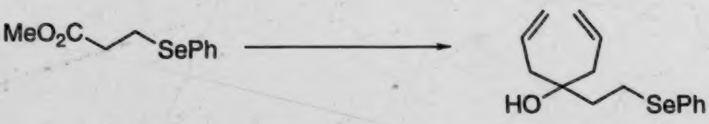
2-Oxabicyclo[3.3.1]nonan-3-one (26.3).



26.2 **26.3**

A solution of Bu_3SnH (0.23 mL, 0.86 mmol) and AIBN (24.1 mg, 0.147 mmol) in PhH (10.5 mL) was added over 10.5 h by syringe pump to a refluxing solution of lactone **26.2** (113 mg, 0.382 mmol) in PhH (50 mL). After the addition, refluxing was continued for an arbitrary period of 1 h. Evaporation of the solvent and flash chromatography (three times) over silica gel (3 x 10 cm), using 5:100 to 1:3 EtOAc-hexane, gave lactone **26.3**[42] (33.4 mg, 62%): ^{1}H NMR ($CDCl_3$, 300 MHz) 1.49-1.80 (m, 6 H), 1.94-2.14 (m, 2 H), 2.23-2.34 (m, 1 H), 2.42-2.54 (m, 1 H), 2.73 (dd, *J* = 18.0, 8.0 Hz, 1 H), 4.70-4.78 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 16.0 (t′), 26.0 (d′), 30.4 (t′), 31.0 (t′), 36.0 (t′), 75.5 (d′), 172.0 (s′).

4-[2-(Phenylseleno)ethyl]-1,6-heptadien-4-ol (27.1).

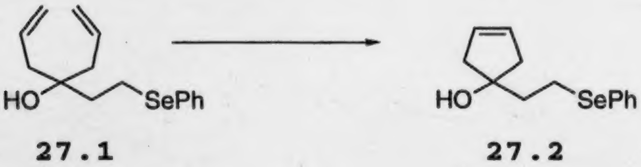


6 **27.1**

Allylmagnesium bromide (1 M in Et_2O, 4.0 mL, 4.0 mmol) was added to a stirred and cooled (0 °C) solution of ester **6**[33] (355 mg, 1.46 mmol) in dry Et_2O (15 mL), and stirring was continued overnight, the cold bath being left in place, but not recharged. The mixture was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with Et_2O (2 x 35 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (8 x 3 cm), using 2:100 to 5:100 EtOAc-hexane, gave alcohol **27.1** (334 mg, 78%) as an oil:

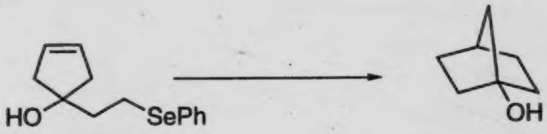
FTIR ($CHCl_3$ cast) 3073 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.74 (s, 1 H), 1.82-1.93 (m, 2 H), 2.16-2.32 (m, 4 H); 2.88-3.06 (m, 2 H); 5.06-5.18 (m, 4 H); 5.72-5.86 (m, 2 H), 7.21-7.32 (m, 3 H), 7.44-7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.5 (t′), 39.8 (t′), 43.5 (t′), 73.9 (s′), 119.1 (t′), 126.8 (d′), 129.1 (d′), 130.3 (s′), 132.5 (d′), 133.2 (d′); exact mass *m/z* calcd for $C_{15}H_{20}O^{80}Se$ 296.06793, found 296.0679.

1-[(Phenylseleno)ethyl]-3-cyclopenten-1-ol (27.2).



$(Cy_3P)_2Cl_2Ru{=}CHPh$ (33 mg, 0.04 mmol) was added to a stirred solution of alcohol **27.1** (93.2 mg, 0.316 mmol) in dry PhH (15 mL), and the solution was refluxed for 6 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (8 x 3 cm), using 3:100 to 10:100 EtOAc-hexane, gave alcohol **27.2** (65 mg, 77%) as an oil: FTIR ($CHCl_3$ cast) 3405 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.97 (s, 1 H), 2.01-2.14 (m, 2 H), 2.37 (d, J = 14.5 Hz, 2 H), 2.54 (d, J = 14.5 Hz, 2 H), 2.97-3.10 (m, 2 H), 5.70 (s, 2 H), 7.17-7.33 (m, 3 H), 7.47-7.57 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.6 (t′), 41.6 (t′), 47.0 (t′), 81.5 (s′), 126.8 (d′), 128.5 (d′), 129.1 (d′), 130.4 (s′), 132.4 (d′); exact mass *m/z* calcd for $C_{13}H_{16}O^{80}Se$ 268.03662, found 268.0365.

Bicylco[2.2.1]heptan-1-ol (27.3).

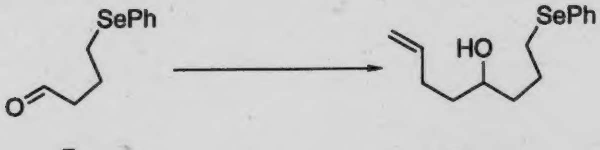


27.2 **27.3**

A solution of Bu_3SnH (0.30 mL, 1.4 mmol) and AIBN (48.2 mg, 0.294 mmol) in PhH (10 mL) was added over 10 h by syringe pump to a refluxing solution of alcohol **27.2** (262 mg, 0.982 mmol) in PhH (50 mL). After the addition, refluxing was continued for an arbitrary period of 30 min. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 17 cm), using 1:100 to 10:100 EtOAc-hexane, gave alcohol **27.3**[39] (60 mg, 54%) as a solid: mp 151-153 °C; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.37-1.68 (m, 9 H), 1.75-1.84 (m, 2 H), 2.06-2.13 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 30.3 (t′), 34.8 (d′), 35.4 (t′), 44.0 (t′), 83.0 (s′).

1-(Phenylseleno)-7-octen-4-one (28.1).

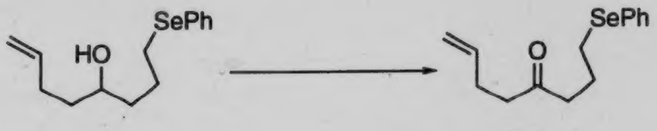
(a) 1-(Phenylseleno)-7-octen-4-ol.



5 **-**

3-Butenylmagnesium bromide (0.5 M in THF, 1.5 mL, 0.75 mmol) was added to a stirred solution of aldehyde **5** (124 mg, 0.546 mmol) in dry Et_2O (13 mL), and stirring was continued overnight. The mixture was quenched with saturated aqueous NH_4Cl (10 mL), and extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 9 cm), using 5:100 to 10:100 EtOAc-hexane, gave 1-(phenylseleno)-7-octen-4-ol (92 mg, 60%) as an oil: FTIR (CH_2Cl_2 cast) 3374 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.44-1.65 (m, 5 H), 1.67-1.95 (m, 2 H), 2.05-2.26 (m, 2 H), 2.93 (d, *J* = 7.6 Hz, 2 H), 3.55-3.67 (m, 1 H), 4.93-5.09 (m, 2 H), 5.75-5.91 (m, 1 H), 7.19-7.32 (m, 3 H), 7.44-7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 26.2 (t′), 27.9 (t′), 30.0 (t′), 36.5 (t′), 37.3 (t′), 70.9 (d′), 114.9 (t′), 126.7 (d′), 129.0 (d′), 130.3 (s′), 132.5 (d′), 138.4 (d′); exact mass *m/z* calcd for $C_{14}H_{20}O^{80}Se$ 284.06793, found 284.0685.

(b) 1-(Phenylseleno)-7-octen-4-one (28.1).



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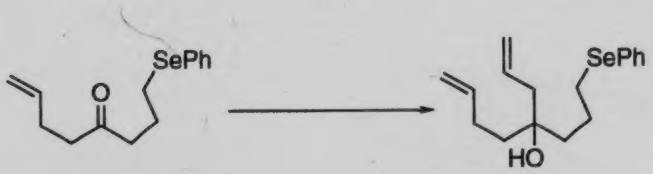
28.1

Pyridine-SO_3 complex (2.21g, 13.9 mmol) in DMSO (15 mL) was added over 20 min to a stirred and cooled (water bath at

20 °C) solution of 1-(phenylseleno)-7-octen-4-ol made in the previous step (1.22g, 4.31 mmol) and Et_3N (12.0 mL, 86.3 mmol) in DMSO (15 mL). After the addition, the solution was stirred for 4.5 h, and then adjusted to pH 3 by addition of 10% hydrochloric acid. The mixture was extracted with Et_2O (2 x 40 mL), and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 10 cm), using 1:20 EtOAc-hexane, gave ketone **28.1** (976 mg, 81%) as an oil: FTIR (CH_2Cl_2 cast) 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.87-2.07 (m, 2 H), 2.21-2.63 (m, 6 H), 2.93 (*t*, J = 7.3 Hz, 2 H), 4.92-5.10 (m, 2 H), 5.68-5.90 (m, 1 H), 7.17-7.33 (m, 3 H), 7.42-7.57 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 23.9 (t′), 27.2 (t′), 27.7 (t′), 41.8 (t′), 42.0 (t′), 115.2 (t′), 126.9 (d′), 129.1 (d′), 130.0 (s′), 132.6 (d′), 137.0 (d′), 209.3 (s′); exact mass *m/z* calcd for $C_{14}H_{18}O^{80}Se$ 282.05228, found 282.0521.

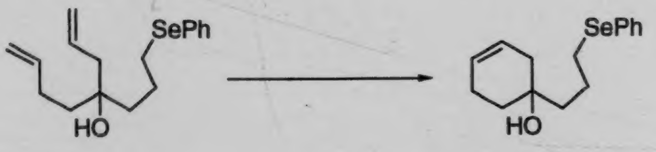
4-[3-(Phenylseleno)propyl]-1,7-octadien-4-ol (28.2).



28.1 **28.2**

Allylmagnesium bromide (1 M in Et_2O, 4.8 mL, 4.8 mmol) was added over 5 min to a stirred and cooled (water bath at 15 °C) solution of ketone **28.1** (931 mg, 3.31 mmol) in dry Et_2O (20 mL), and stirring was continued overnight. The mixture was quenched with saturated aqueous NH_4Cl (25 mL), and extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 11 cm), using 1:100 to 5:100 EtOAc-hexane, gave alcohol **28.2** (830 mg, 78%) as an oil: FTIR (CH_2Cl_2 cast) 3456 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.34-1.88 (m, 7 H), 1.98-2.31 (m, 4 H), 2.92 (t, *J* = 7.1 Hz, 2 H), 4.82-5.23 (m, 4 H), 5.64-5.96 (m, 2 H), 7.13-7.38 (m, 3 H), 7.42-7.58 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 24.2 (t′), 27.9 (t′), 28.4 (t′), 38.2 (t′), 39.1 (t′), 43.8 (t′), 73.6 (s′), 114.6 (t′), 118.9 (t′), 126.8 (d′), 129.0 (d′), 130.4 (s′), 132.5 (d′), 133.5 (d′), 138.7 (d′); exact mass *m/z* calcd for $C_{17}H_{24}O^{80}Se$ 324.09924, found 324.1001.

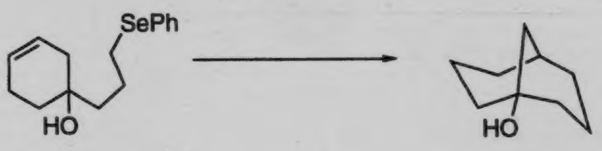
1-[3-(Phenylseleno)propyl]-3-cyclohexen-1-ol (28.3).



28.2 **28.3**

$(Cy_3P)_2Cl_2Ru{=}CHPh$ (133 mg, 0.161 mmol) was added to a stirred solution of alcohol **28.2** (616 mg, 1.91 mmol) in dry PhH (60 mL), and the solution was stirred overnight at 65 °C. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 13 cm), using 2:100 to 10:100 EtOAc-hexane, gave alcohol **28.3** (482 mg, 86%) as an oil: FTIR (CH_2Cl_2 cast) 3438 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.49-1.68 (m, 5 H), 1.74-1.91 (m, 2 H), 1.94-2.26 (m, 4 H), 2.92 (t, J = 7.2 Hz, 2 H), 5.54-5.62 (m, 1 H), 5.66-5.76 (m, 1 H), 7.16-7.31 (m, 3 H), 7.45-7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 22.5 (t′), 23.6 (t′), 28.4 (t′), 33.0 (t′), 37.8 (t′), 41.0 (t′), 69.8 (s′), 124.2 (d′), 126.4 (d′), 126.5 (d′), 128.8 (d′), 130.3 (s′), 132.3 (d′); exact mass *m/z* calcd for $C_{15}H_{20}O^{80}Se$ 296.06793, found 296.0679.

Bicyclo[3.3.1]nonan-1-ol (28.4).[39]



28.3 **28.4**

A solution of Bu_3SnH (100 µl, 0.372 mmol) and AIBN (16 mg, 0.098 mmol) in PhH (10 mL) was added over 10 h by syringe pump to a refluxing solution of alcohol **28.3** (100 mg, 0.339 mmol) in PhH (20 mL). After the addition, some starting material still remained (TLC control, silica, 1:4 EtOAc-hexane). Therefore, a solution of Bu_3SnH (60 µL, 0.223 mmol) and AIBN (10 mg, 0.061 mmol) in PhH (6 mL) was added over 4.5 h (syringe pump). After this addition, all starting material had reacted (TLC control, silica, 1:4 EtOAc-hexane). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 11 cm), using 1:100 to 5:100 EtOAc-hexane, gave bicyclic alcohol **28.4**[39] (24.1 mg, 51%) as a solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47-1.69 (m, 11 H), 1.78-1.99 (m, 4 H), 2.13-2.21 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 23.0, 30.2, 32.3, 39.7, 43.7, 69.5.

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26 Other oxidation methods: (a) Baudat, R.; Petrzilka, M. *Helv. Chim. Acta* **1979**, *62*, 1406. (b) Barton, D. H. R.; Lester, D. J.; Motherwell, W. B.; Papoula, M. T. B.; *J. Chem. Soc., Chem. Commun.* **1980**, 246. (c) Posner, G. H.; Chapdelaine, M. J. *Tetrahedron Lett.* **1977**, 3227. (d) Shimizu, M.; Urabe, H.; Kuwajima, I. *Tetrahedron Lett.* **1981**, *22*, 2183. (e) Lucchetti, J.; Krief, A. *C. R. Acad. Sci. Ser C* **1979**, *288*, 537.

27 Sulfides and disulfides have been subjected to RCM, using a *molybdenum* catalyst; in some experiments a ruthenium catalyst [$(Cy_3P)_2Cl_2Ru{=}CHCH{=}CPh_2$] was unsatisfactory (reference 28), as was $(Cy_3P)_2Cl_2Ru{=}CHPh$

(Reference 29).

28 E.g. (a) Shon, Y.-S.; Lee, T. R. *Tetrahedron Lett.* **1997**, *38*, 1283. (b) Armstrong, S. K.; Christie, B. A. *Tetrahedron Lett.* **1996**, *37*, 9373.

29 Barrett, A. G. M.; Ahmed, M.; Baker, S. P.; Baugh, S. P. D.; Braddock, D. C.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 3716.

30 For a rare example of RCM of a sulfide, using $(Cy_3P)_2Cl_2Ru{=}CHPh$, see: Barrett, A. G. M.; Baugh, S. P. D.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *63*, 7893.

31 For an extensive table of functional group-catalyst compatibility, see: Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.

32 (a) Clive, D. L. J.; Bergstra, R. J. *J. Org. Chem.* **1990**, *55*, 1786. (b) Bigogno, C.; Danieli, B.; Lesma, G.; Passarella, D. *Heterocycles* **1995**, *41*, 973.

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34 For one of several recent reviews, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

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37 Gosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651.

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40 Clive, D. L. J.; Wickens, P. L.; Sgarbi, P. W. M. *J. Org. Chem.* **1996**, *61*, 7426.

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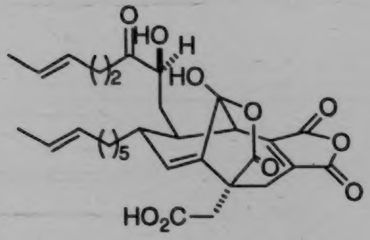
Chapter 3

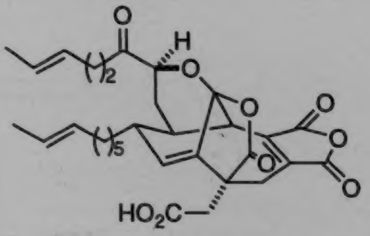
Synthetic studies on CP-225,917

Introduction

Pfizer scientists reported the isolation of two natural products CP-225,917 (**1**) and CP-263,114 (**2**) as fungal metabolites extracted from juniper twigs found in Texas.[1] These substances exhibit impressive cholesterol-lowering properties through inhibition of squalene synthase.[1,2] Furthermore, they inhibit ras farnesyl transferase, an enzyme implicated in the development of cancer, and as such, they stand as leads to potential drugs for cancer chemotherapy.[1,3]



1 CP-225,917



2 CP-263,114

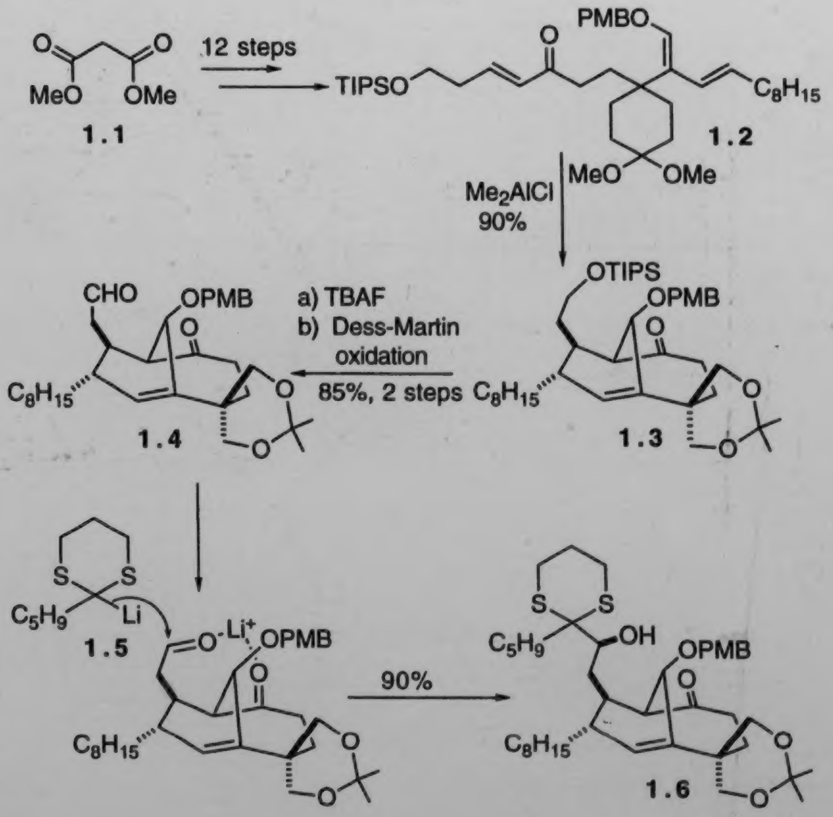
In addition to these interesting biological activities, the two compounds have a unique polycyclic skeleton that consists of a bridgehead olefin, a maleic anhydride moiety, as well as a collection of unusual and densely packed, labile functional groups. The chemical architecture of CP-molecules and their interesting bioactivities have stimulated considerable efforts towards establishing routes for the total synthesis of the two molecules.[4]

In 1999, the Nicolaou group reported the first total synthesis of CP-225,917 (**1**) and CP-263,114 (**2**),[5] and in the following year they determined the absolute configuration of the two compounds by way of an asymmetric synthesis of an advanced intermediate in their total synthesis.[6] It turned out that their samples of **1** and **2** were actually the enantiomers of the natural compounds. More recently, three additional and elegant total syntheses have been achieved by the Shair,[7] Fukuyama,[8] and Danishefsky[9] groups. The latter described the synthesis of racemic **1**, and the Shair and Fukuyama groups made optically active **2**, Fukuyama's work leading to the correct absolute stereochemistry and Shair's to the unnatural enantiomer. Surprisingly, neither Shair nor Fukayama claim that their work also constitutes a synthesis of **1**, since by that time Nicolaou had described the synthesis of **1** by way of **2**.

1. Nicolaou's Approaches

Nicolaou and coworkers converted dimethyl malonate (**1.1**) into the triene **1.2** in twelve steps (Scheme 1). This triene underwent intramolecular Diels-Alder reaction in the presence of a catalytic amount of Me_2AlCl at 0°C to afford the key bicyclic core **1.3** in the impressive yield of 90%. The fact that **1.3** was prepared in only 13 steps with a total yield of about 10% enabled Nicolaou's group to make multigram quantities of this intermediate, and this availability made extensive explorations from this compound feasible.

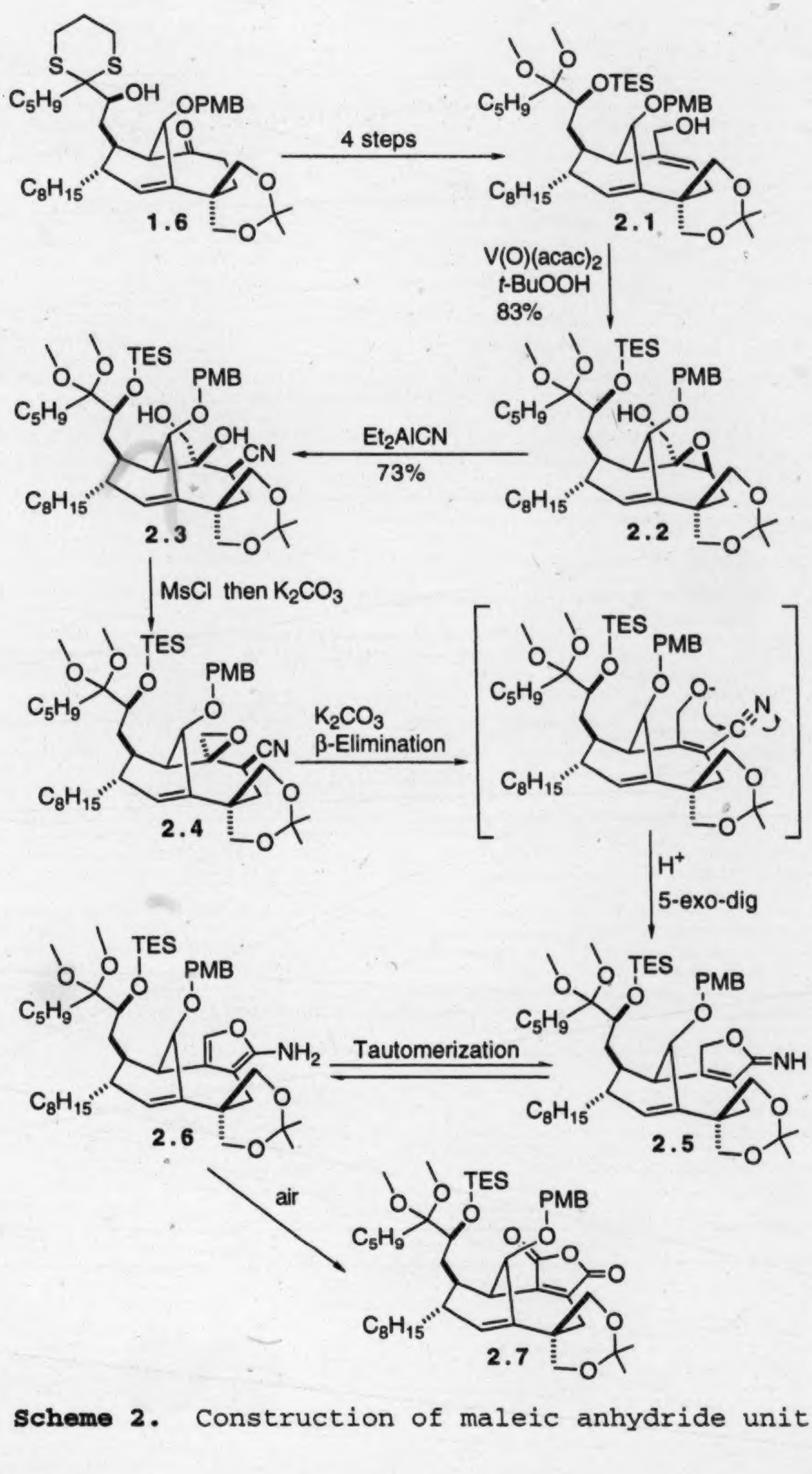
Aldehyde **1.4** was prepared in two steps from **1.3** in 85% yield. Treatment of **1.4** with the lithiodithiane **1.5** proceeded with an 11:1 diastereoselectivity to give the desired alcohol **1.6** as the major product.



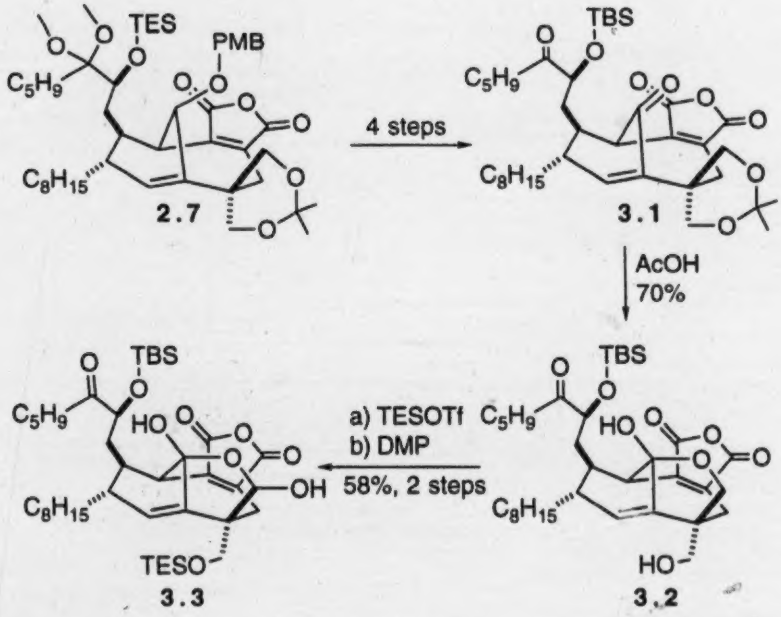
Scheme 1. Construction of the core bicycle and installation of the side chain.

The next task was installation of the maleic anhydride (Scheme 2). After the CP core **1.6** had been converted into the allylic alcohol **2.1** in 4 steps, vanadium-assisted epoxidation generated selectively the corresponding β-epoxide **2.2**. Rupture of the epoxide with Nagata's reagent [Et_2AlCN] led to an unexpected *syn* epoxide ring-opening to furnish diol **2.3**. Exposure of **2.3** to MsCl/Et_3N, followed by treatment of the resulting mesylate with K_2CO_3 in MeOH provided cyano epoxide **2.4**, which underwent a cascade of reactions to give the anhydride **2.7**. The yield from **2.3** to **2.7** was 56%.

The anhydride **2.7** was converted into enone **3.1** in 4 steps (Scheme 3). Removal of the acetonide group by the action of AcOH generated two free hydroxymethyl groups. The upper hydroxymethyl group cyclized onto the bridgehead carbonyl, furnishing hemiketal **3.2** in 70% yield. Protection of the lower hydroxymethyl group by silylation with $Et_3SiOSO_2CF_3$, followed by oxidation with DMP in refluxing PhH, generated hydroxy lactol **3.3**.



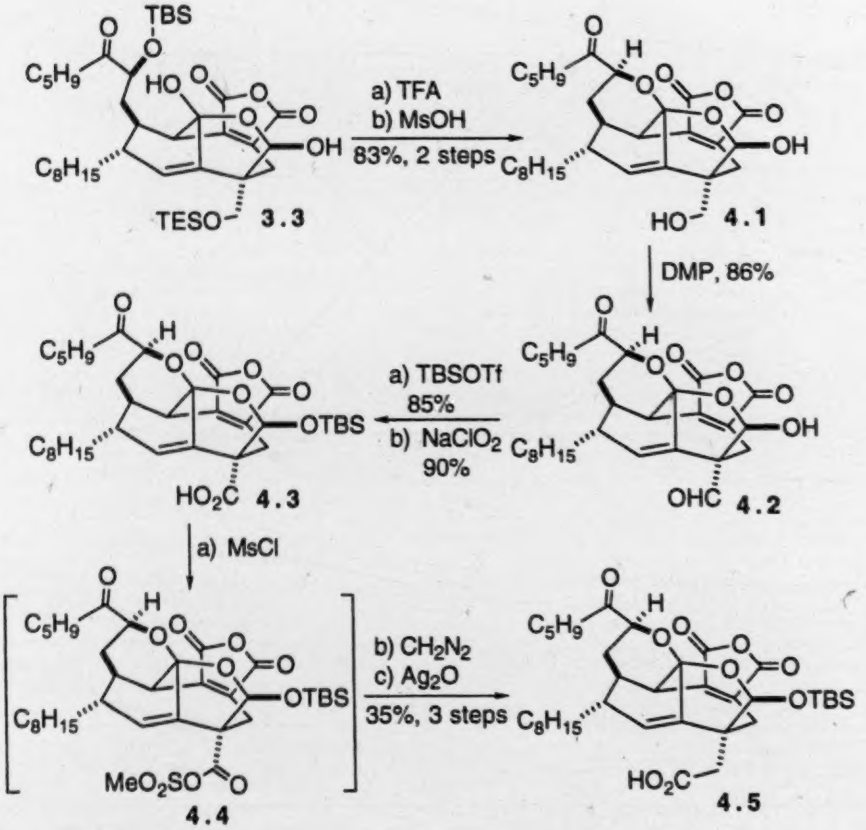
Scheme 2. Construction of maleic anhydride unit.



Scheme 3. Construction of hydroxy lactol **3.3**.

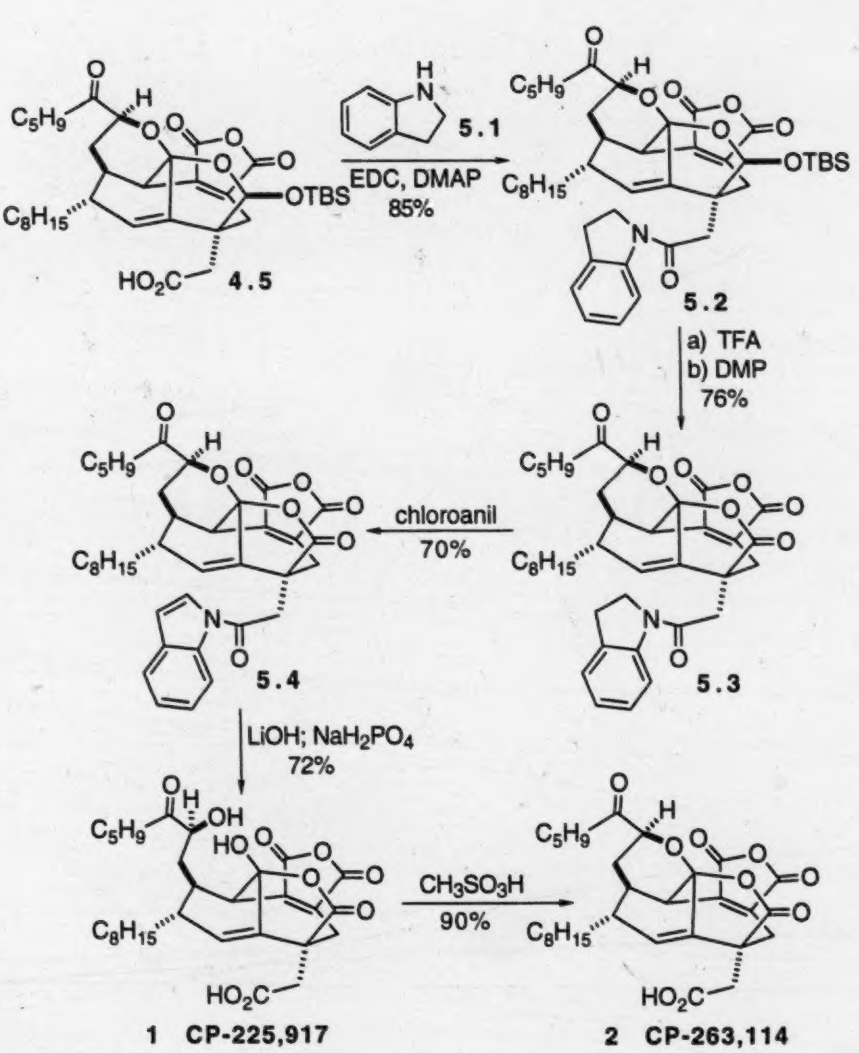
Both silicon groups of **3.3** were then removed by the action of aqueous CF_3CO_2H in CH_2Cl_2 (Scheme 4). Treatment of the resulting triol with $MeSO_3H$ led to formation of the pyran-lactol **4.1**. Selective oxidation of **4.1** with DMP in benzene generated aldehyde lactol **4.2**. After lactol **4.2** had been protected as its TBS ether, oxidation of the aldehyde group with $NaClO_2$ provided the hindered acid **4.3**. Activation of the acid was accomplished by conversion into the reactive acyl mesylate **4.4** with MsCl/Et_3N at 0 °C. The mesylate reacted with diazomethane, furnishing a diazoketone which underwent Wolff rearrangement to give the homologated acid **4.5**.

The acid was protected as an amide (**5.2**) by coupling with indoline in the presence of EDC and DMAP (Scheme 5).



Scheme 4. Synthesis of homologated acid **4.5**.

Removal of the TBS group, followed by oxidation of the resulting lactol with DMP, led to lactone **5.3**. The indoline unit in **5.3** was oxidized to the corresponding indole **5.4** by the action of *p*-chloranil, thereby generating a labile amide. Hydrolysis of **5.4**, using LiOH, led to a cascade of reactions that furnished CP-225,917. Treatment of CP-225,917 (**1**) with methanesulfonic acid provided CP-263,114 (**2**) which, presumably, is an intermediate in the conversion of **5.4** into **1**.

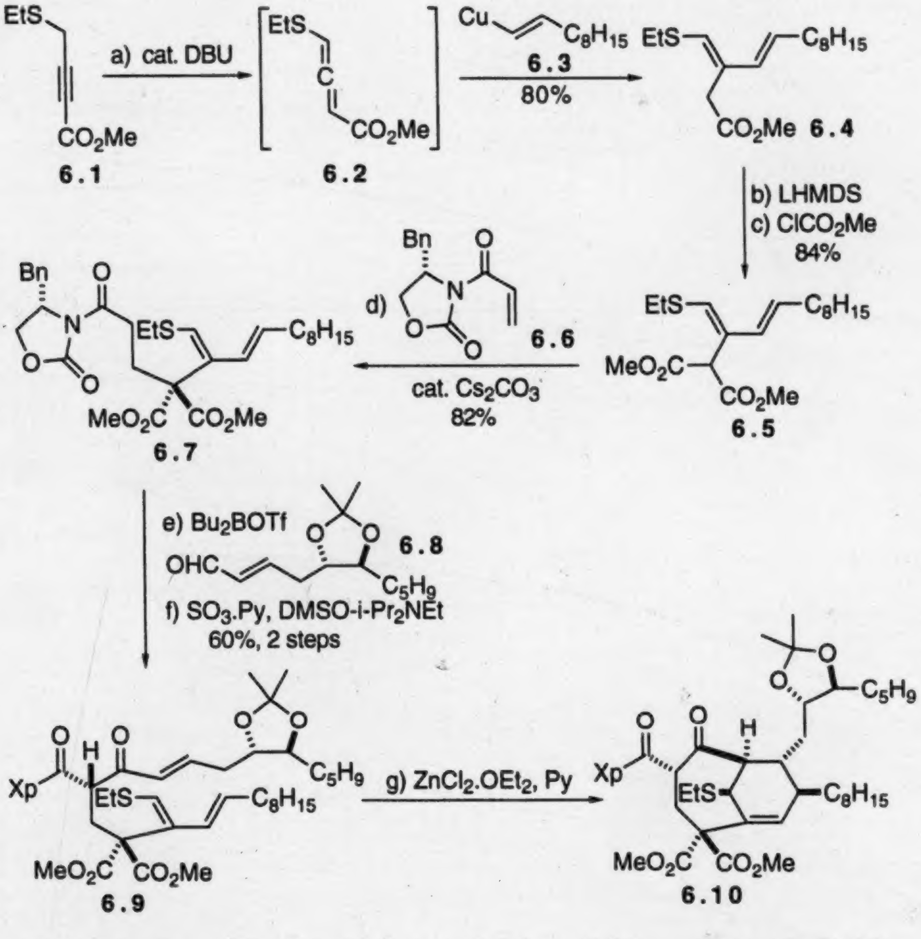


Scheme 5. Final steps in the synthesis of CP-225,917 (**1**) and CP-263,114 (**2**).

2. Fukuyama's enantioselective total synthesis of CP-263,114 (2)

Fukuyama also used an intramolecular Diels-Alder reaction to prepare his key intermediate, which in this case was the strained bicyclic compound **6.10**.[8] This substance was made enantioselectively in only 6 steps and is a more advanced intermediate than Nicolaou's Diels-Alder's adduct **1.3**.

Synthesis of **6.10** commenced with methyl 4-ethylthio-2-butynoate **6.1** (Scheme 6). Isomerization of **6.1** in the presence of DBU provided the allenic ester **6.2**. Addition of the alkenylcopper **6.3** to the allenic ester generated the desired (*Z,Z*)-diene **6.4** with high stereoselectivity and good yield (80%). A second methoxycarbonyl group was then introduced, and the resulting malonate (**6.5**) was used for

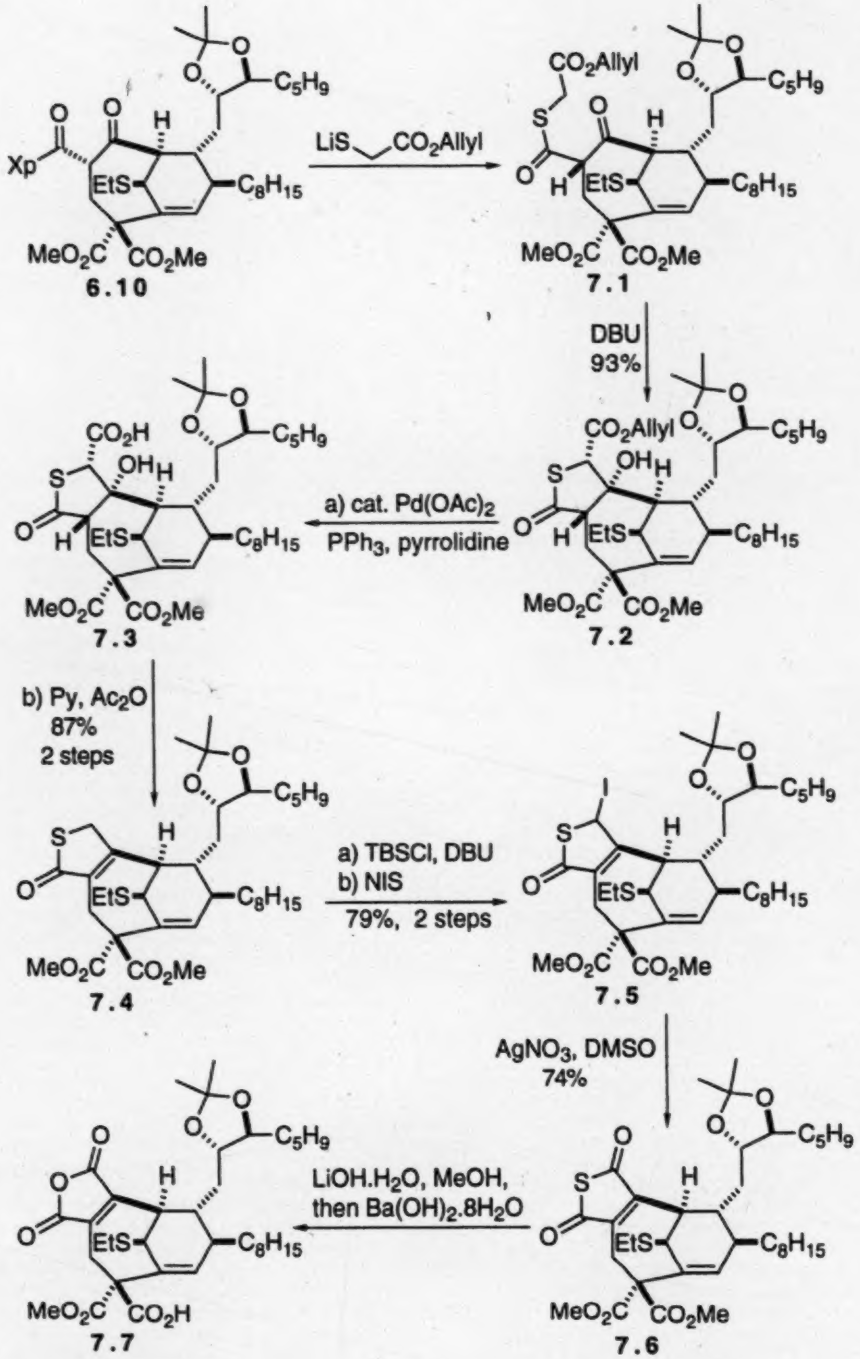


Scheme 6. Construction of bicyclic compound **6.10**.

conjugate addition to *N*-acryloyl-(*S*)-4-benzyloxazolidinone **6.6**, furnishing **6.7**. Boron-mediated diastereoselective aldol condensation of **6.7** with aldehyde **6.8** provided an alcohol and oxidation then gave enone **6.9**. Smooth intramolecular Diels-Alder reaction of enone **6.9** in the presence of $ZnCl_2$ provided predominantly the desired bicyclic compound **6.10**.

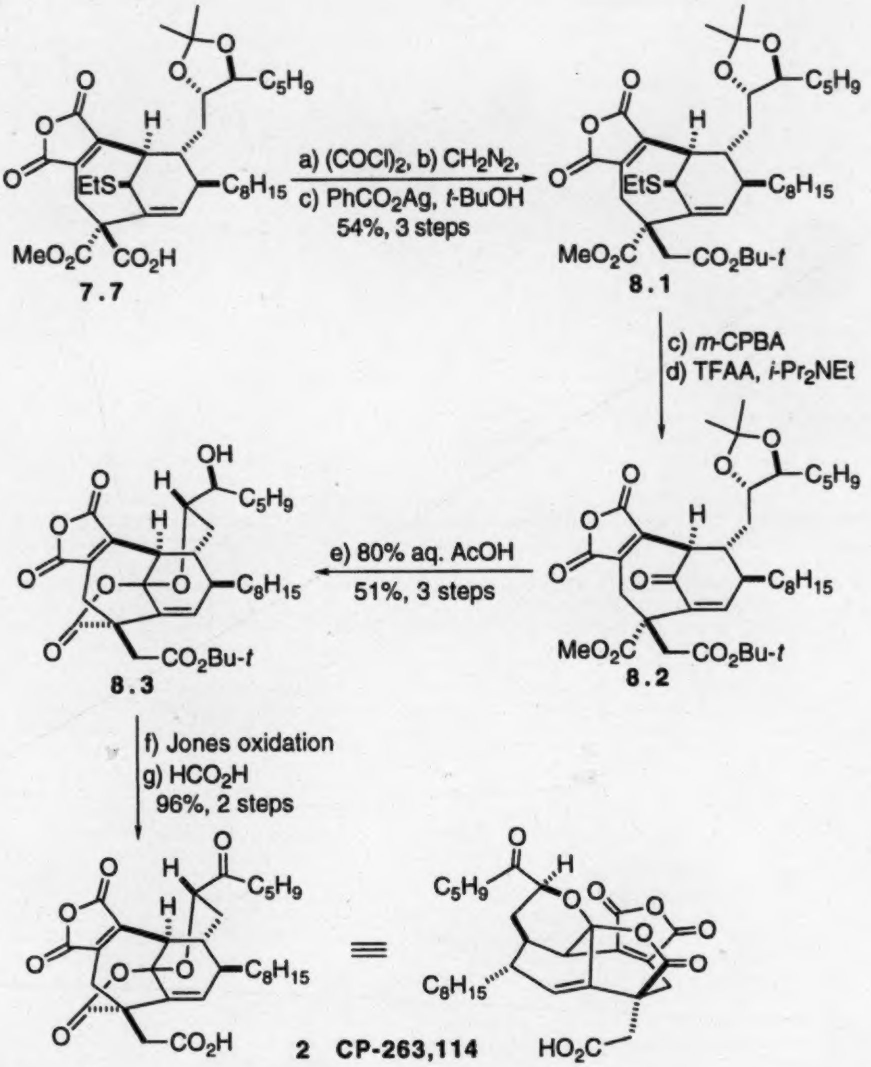
The next step was the synthesis of the maleic anhydride unit (Scheme 7). Cleavage of the Evans' chiral auxiliary from **6.10** with a lithium thiolate afforded thiol ester **7.1** in 53% yield from **6.9**. Intramolecular cyclization of **7.1** in an aldol condensation in the presence of DBU gave only alcohol **7.2** (93%). Removal of the allylic group from **7.2**, using $Pd(OAc)_2$, gave acid **7.3**. This was heated in a mixture of acetic anhydride and pyridine for 1 h, to induce dehydration and decarboxylation, giving directly the thiobutenolide **7.4**. Silylation of **7.4** with TBSCl and DBU, followed by oxidation of the resultant 2-silyloxythiophene with NIS, provided the 5-iodothiobutenolide **7.5**. Treatment of **7.5** with $AgNO_3$ in DMSO at 50 °C gave the thiomaleic anhydride **7.6**. Successive treatment of **7.6** with lithium hydroxide and barium hydroxide in a one-pot process caused selective hydrolyses of the thiomaleic anhydride and the less hindered methyl ester, furnishing the monocarboxylic acid **7.7**.

Homologation of acid **7.7** was accomplished by Arndt-Eistert reaction to give ester **8.1** (Scheme 8). The sulfide



Scheme 7. Synthesis of maleic anhydride **7.7**.

group in **8.1** was oxidized carefully with *m*-CPBA to the sulfoxide and Pummerer rearrangement then gave ketone **8.2**. Upon treatment with 80% aqueous acetic acid, cleavage of the acetonide was followed by cyclization, providing γ-lactone-acetal **8.3**. The secondary alcohol of **8.3** was oxidized to the corresponding ketone, and deprotection of the *t*-butyl



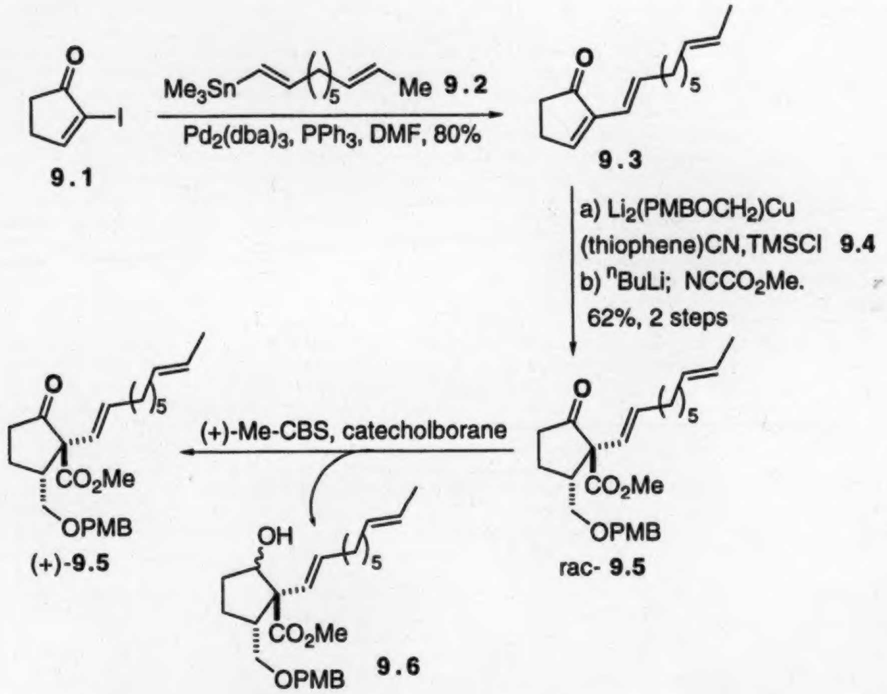
Scheme 8. Final steps of Fukuyama's approach to (-)-CP-263,114.

ester provided (-)-CP-263,114.

3. Shair's synthesis of (+)-CP-263,114 (2)

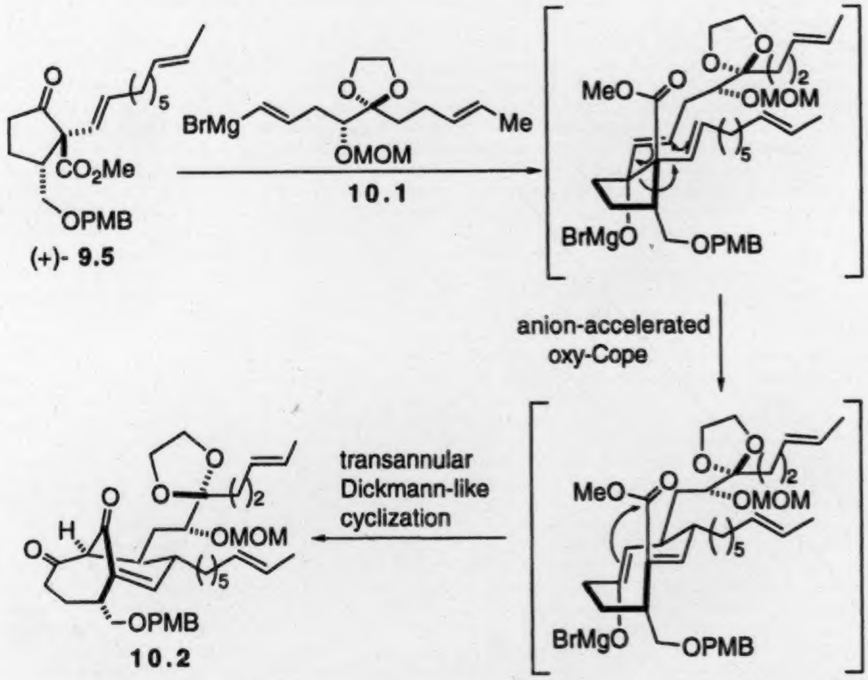
Shair's group used a remarkable fragment coupling/tandem cyclization to obtain the core structure of **2**.[7]

A Pd-catalyzed cross-coupling between iodo enone **9.1** and vinyl stannane **9.2** provided enone **9.3** (Scheme 9). Michael addition of cuprate **9.4** to **9.3** gave the expected ketone enolate, and *C*-acylation, using Mander's reagent, generated the highly functionalized cyclopentanone *rac*-**9.5**. Kinetic resolution of *rac*-**9.5** was accomplished by treatment with CBS-catecholborane so as to afford **9.5** and the alcohol **9.6** (of unspecified stereochemistry).


9.1
Me3Sn
5
Me 9.2
Pd2(dba)3, PPh3, DMF, 80%
9.3
a) Li2(PMBOCH2)Cu (thiophene)CN,TMSCl 9.4
b) nBuLi; NCCO2Me.
62%, 2 steps
(+)-Me-CBS, catecholborane
CO2Me
OPMB
(+)-9.5
OH
9.6
rac- 9.5

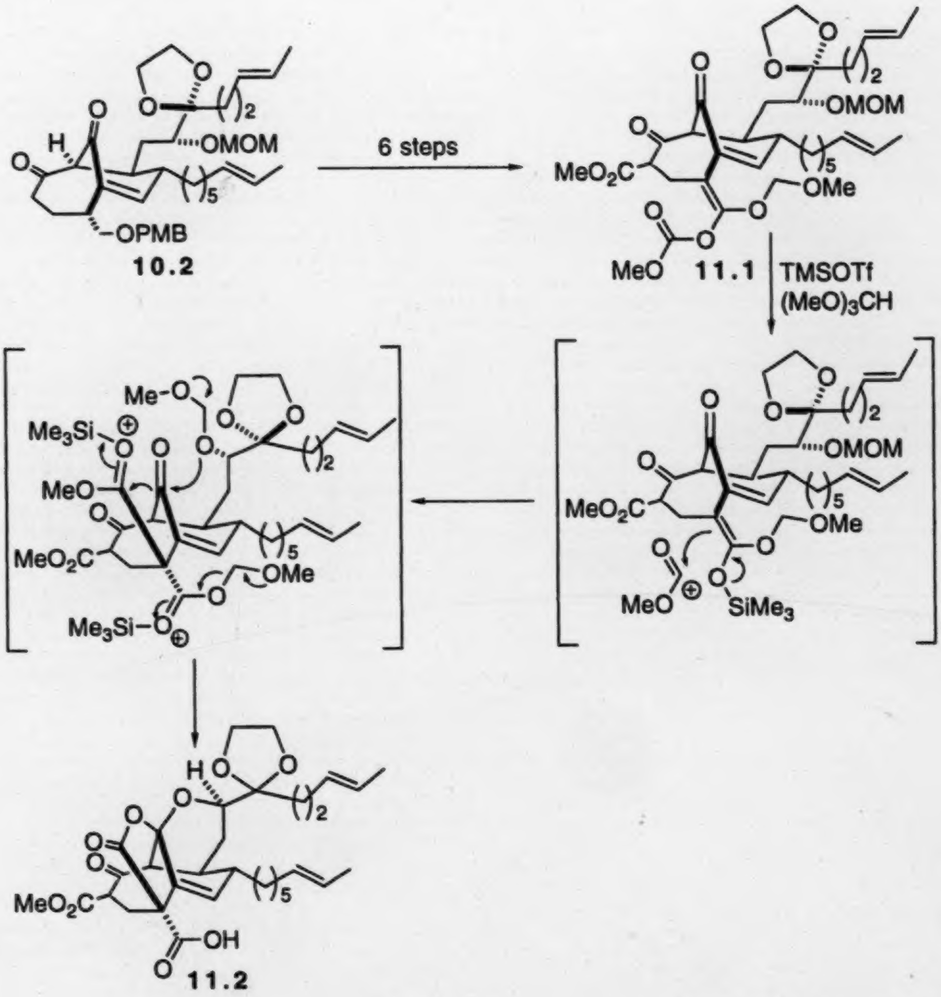
Scheme 9. Early steps of Shair's approach.

Coupling of the cyclopentanone (+)-**9.5** with Grignard reagent **10.1** provided a bromomagnesium alkoxide, which underwent concomitant anion-accelerated oxy-Cope rearrangement, furnishing an enolate. The latter underwent spontaneous transannular Dieckmann cyclization to give the highly fuctionalized bicyclic compound **10.2** (Scheme 10). This remarkable stereospecific fragment coupling/tandem cyclization afforded **10.2** in a yield of 53%.



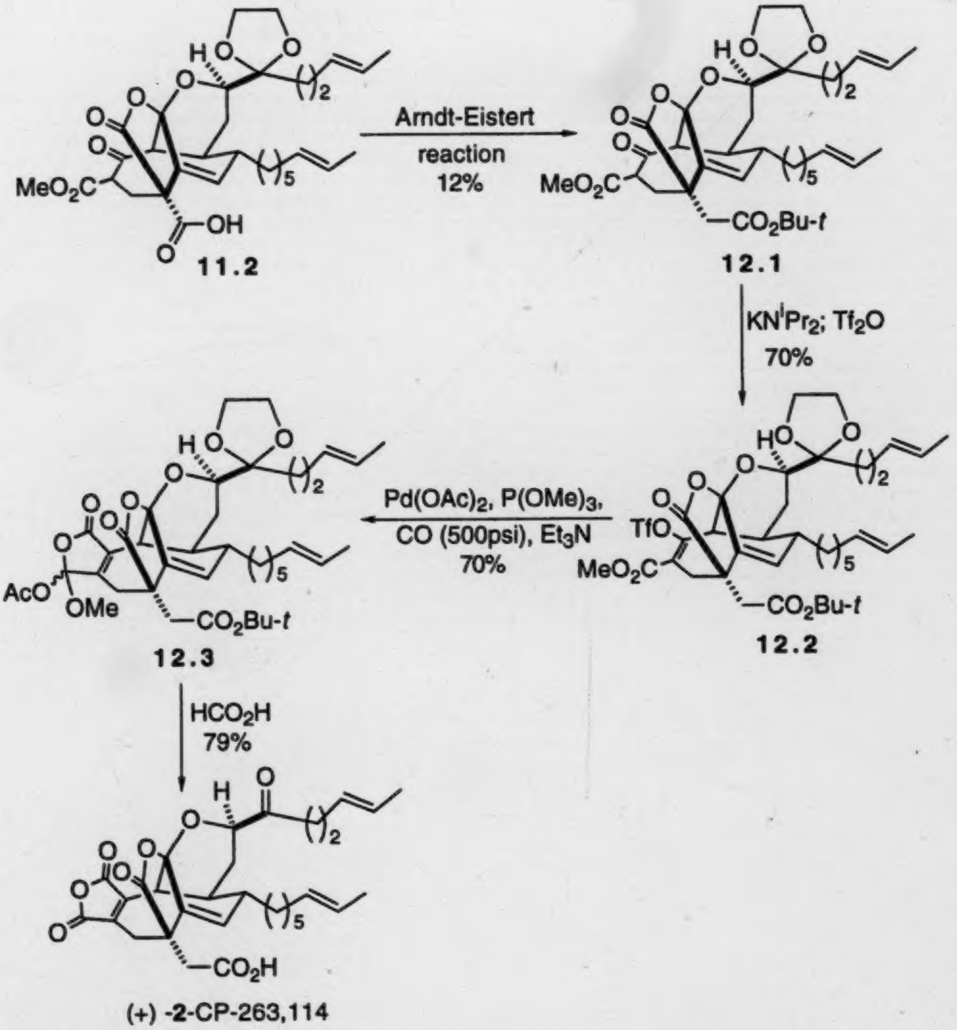
Scheme 10. Oxy-Cope rearrangement and transannular Dieckmann cyclization.

Compound **10.2** was converted into enol carbonate **11.1** in 6 steps (Scheme 11). Upon treatment with $Me_3SiOSO_2CF_3$ and $(MeO)_3CH$, **11.1** underwent a series of reactions that included a Fries-like rearrangement, bicyclization and deprotection, affording **11.2**.



Scheme 11. Synthesis of lactone acid **11.2**.

Due to the high sensitivity of the resulting γ-lactone, homologation of acid **11.2**, using the Arndt-Eistert protocol, gave **12.1** in a low yield (12%) (Scheme 12). Compound **12.1** was converted into the triflate **12.2** upon treatment with *i*-Pr_2NK and $(CF_3SO_2)_2O$. Carbonylation of **12.2**, using a catalyst derived from Pd(OAc)$_2$ and P(OMe)$_3$, gave rise to anhydride orthoester **12.3**, and global deprotection of **12.3** with HCO$_2$H provided (+)-CP-263,114. The final product was not absolutely pure, however.

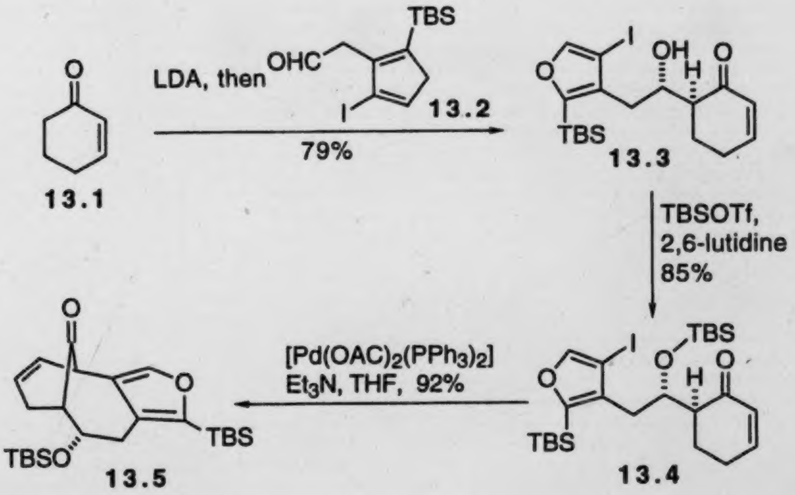

11.2
Arndt-Eistert reaction 12%
12.1
KN^{i}Pr$_2$; Tf$_2$O 70%
12.2
Pd(OAc)$_2$, P(OMe)$_3$, CO (500psi), Et$_3$N 70%
12.3
HCO$_2$H 79%
(+) -2-CP-263,114
MeO$_2$C
CO$_2$Bu-t
TfO
AcO
OMe
CO$_2$H
OH

Scheme 12. Final steps of the total synthesis by Shair.

4. Danishefsky's approach to CP molecules[9]

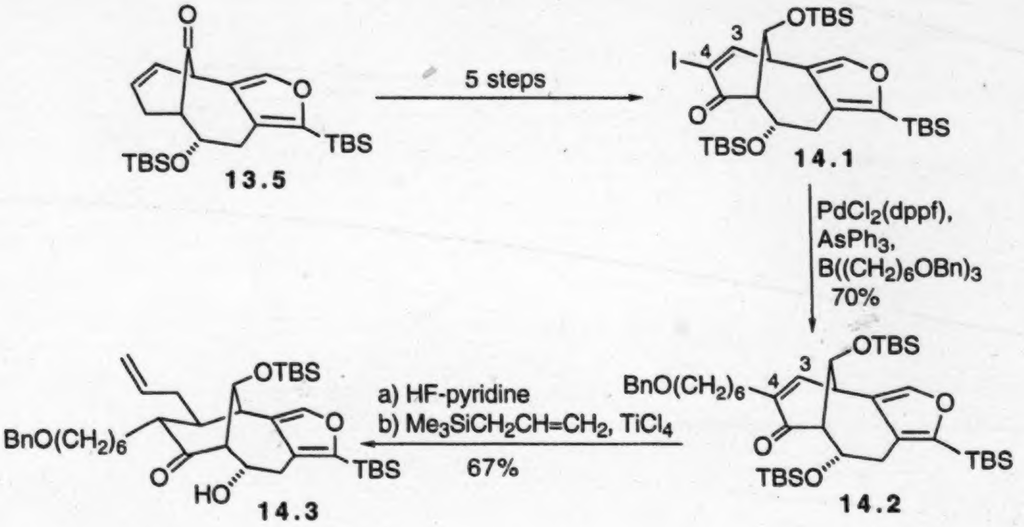
Danishefsky started with aldol condensation of 2-

cyclohexenone (**13.1**) with aldehyde **13.2**, furnishing the desired alcohol **13.3** in 79% yield (Scheme 13). The hydroxyl group was protected as its TBS ether, and ring closure, using an intramolecular Heck vinylation, provided the bicyclic compound **13.5** in 92% yield.



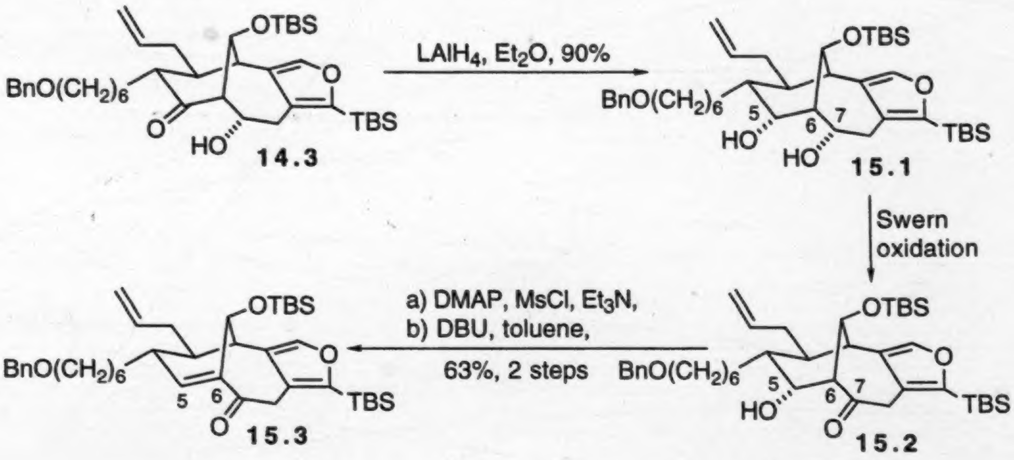
Scheme 13. Synthesis of bicyclic core structure **13.5**.

Compound **13.5** was converted into iodo enone **14.1** in 5 steps (Scheme 14). The C-4 side chain was attached to **14.1**, using a B-alkyl Suzuki reaction, so as to generate **14.2**. After selective removal of the TBS group to release the free hydroxyl at C-7, the C-3 side chain was installed using Sakurai conjugate addition, thereby giving the adduct **14.3** with the desired trans stereochemical relationship at C-3 and C-4.



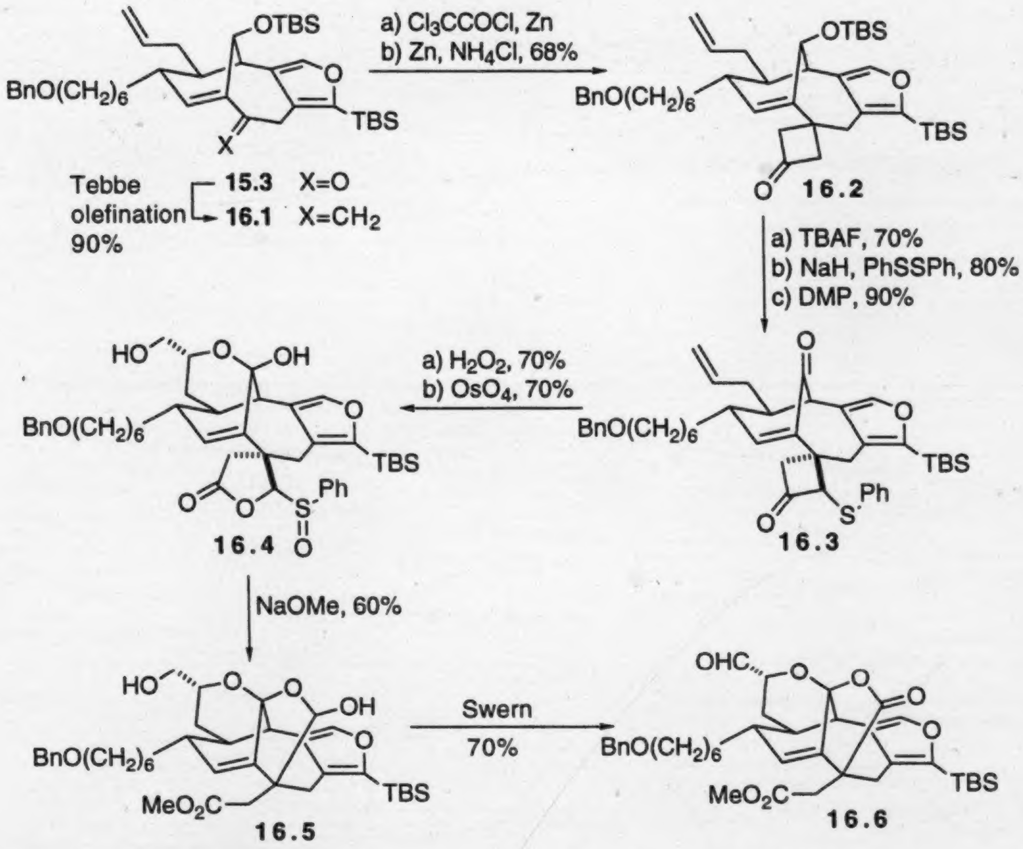
Scheme 14. Incorporation of side-chain at C-3 and C-4.

Reduction of **14.3** with $LiAlH_4$ gave **15.1** (Scheme 15), and selective oxidation of the alcohol functionality at C-7 using the Swern reaction afforded **15.2**. Mesylation of the hydroxyl group at C-5 was followed by elimination of the mesyloxy group by the action of DBU. This experiment furnished **15.3** with the bridgehead double bond.



Scheme 15. Introduction of bridgehead double bond.

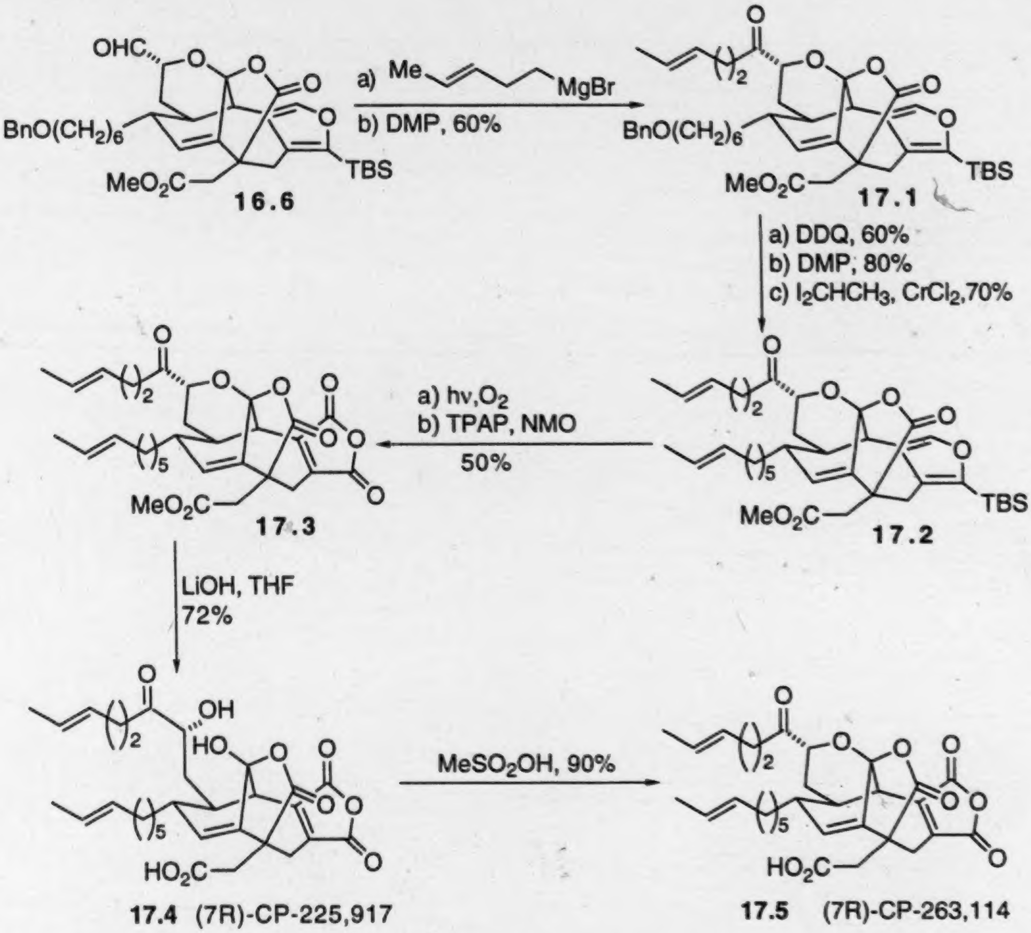
Tebbe olefination of **15.3** gave alkylidene **16.1** (Scheme 16). Dichloroketene selectively reacted with this olefin in a [2+2] cycloaddition in the presence of the allyl group, furnishing a dichlorocyclobutanone. The geminal chlorines were removed reductively, furnishing **16.2**. After cleavage of the TBS group, **16.2** underwent base-induced sulfenylation to give the corresponding substituted cyclobutanone, and oxidation of the secondary alcohol with DMP afforded **16.3**. Regiospecific Baeyer-Villiger reaction was followed by oxidation of the sulfenyl lactone to the corresponding



Scheme 16. Construction of γ-lactone.

sulfoxide. Selective dihydroxylation of the terminal allyl group in the presence of the bridgehead double bond led to formation of lactol **16.4**. Treatment of **16.4** with MeONa resulted in a cascade of rearrangements, providing **16.5**, and Swern oxidation then gave lactone **16.6**.

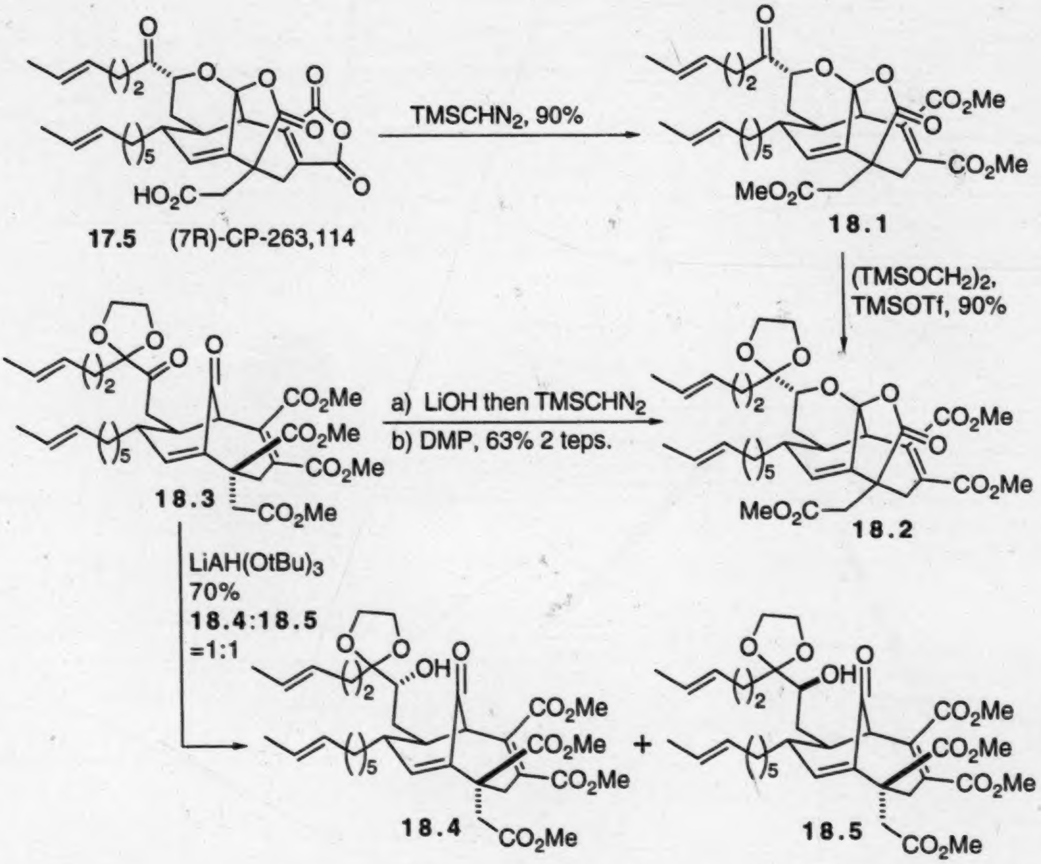
Pentenylation of **16.6**, followed by oxidation of the resulting alcohol, gave rise to **17.1** (Scheme 17). Cleavage of the benzyl group with DDQ released the primary alcohol, which was oxidized to afford the aldehyde. Coupling of the aldehyde with I_2CHCH_3, catalyzed by $CrCl_2$, provided **17.2**. Photooxidation of the silyl furan unit in **17.2** then afforded a γ-hydoxylactone which was oxidized further with TPAP/NMO to the maleic anhydride **17.3**. Hydrolysis of **17.3** with LiOH provided **17.4**, which is the C-7 epimer of CP-225,917 (but was later found to be a natural product), and this was converted into **17.5** (an epimer of CP-263,114 and also a natural product) by the action of $MeSO_3H$.



Scheme 17. Elaboration of side chains and synthesis of maleic anhydride moiety.

Reaction of **17.5** with Me_3SiCHN_2 gave the methyl ester **18.1** (Scheme 18). The ketone group in **18.1** was protected as a ketal (**18.2**), and this was converted into **18.3** in two steps. Reduction of **18.3** with LiAlH(OBu-*t*)$_3$ afforded **18.4** and **18.5** in a 1:1 ratio.

While **18.4** can be recycled through an oxidation-reduction process, hydrolysis of the methyl ester units in

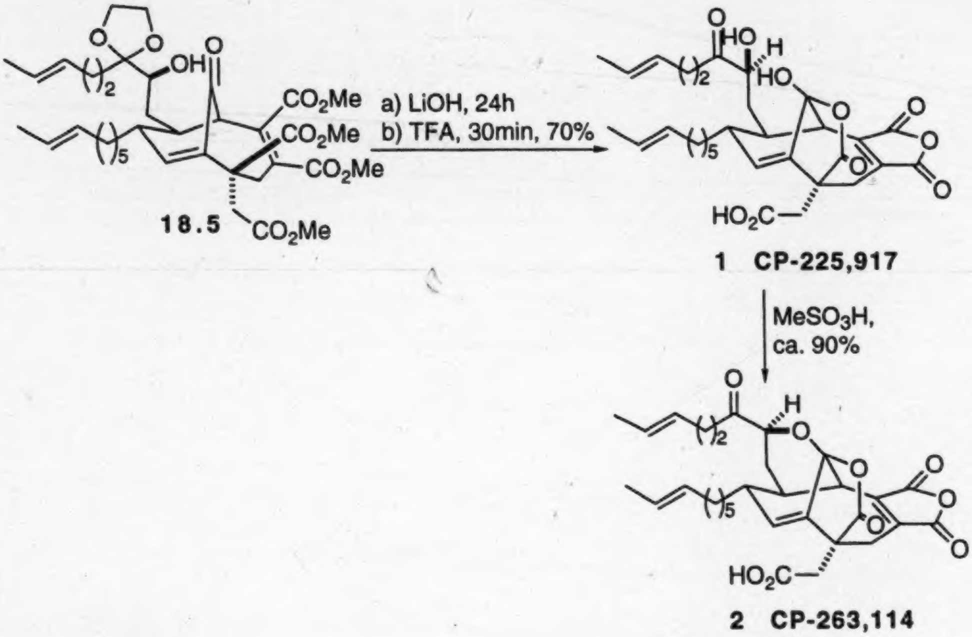


Scheme 18. Arrival at key intermediates **18.4** and **18.5**.

18.5 and treatment with TFA regenerated the anhydride and lactone ring systems, finally providing CP-225,917 (Scheme 19). Treatment of CP-225,917 with MeSO$_3$H gave CP-263,114 (Scheme 19).

Conclusion

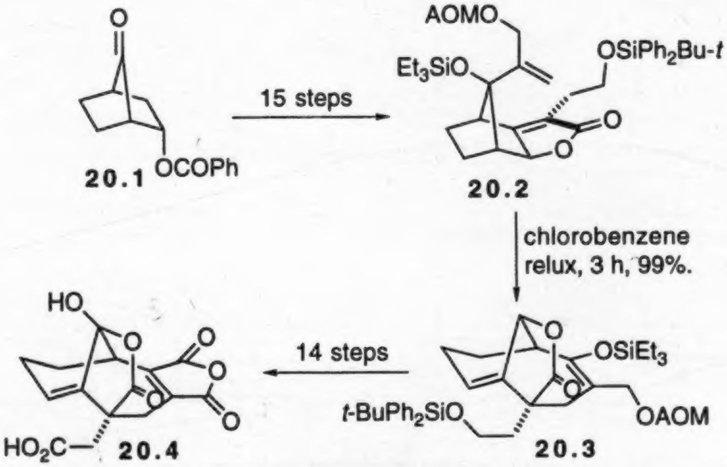
It is clear from the above summary of synthetic work on the two main CP molecules that the compounds present a very difficult challenge, and there is much room for the development of more efficient approaches.



Scheme 19. Final steps in the Danishefsky synthesis.

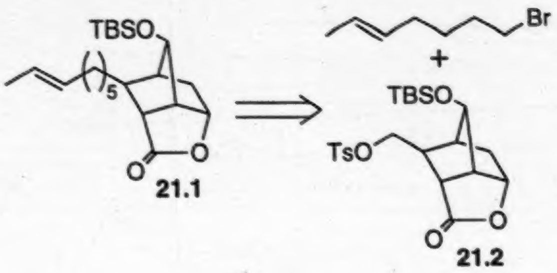
Results and Discussion

The synthetic approach towards **1** and **2** being explored in this laboratory is based on the oxy-Cope rearrangement. In 2001, the synthesis of the racemic tetracyclic core of **1** (Scheme 20) was reported from this laboratory.[10] The readily available bicyclic ketone **20.1** was converted into the strained lactone **20.2** in 15 steps. This lactone underwent efficient thermal siloxy-Cope rearrangement (99%) to the bridgehead olefinic lactone **20.3**, which was then elaborated into **20.4**, the racemic tetracyclic core of **1**, in 14 steps.



Scheme 20

However, **20.4** does not have the two sidechains that are present in **1**, and, in order to complete the total synthesis of **1**, we need to introduce these sidechains at an appropriate stage. To this end, my initial assignment was to prepare the lactone **21.1**, containing the 8-carbon olefinic sidechain

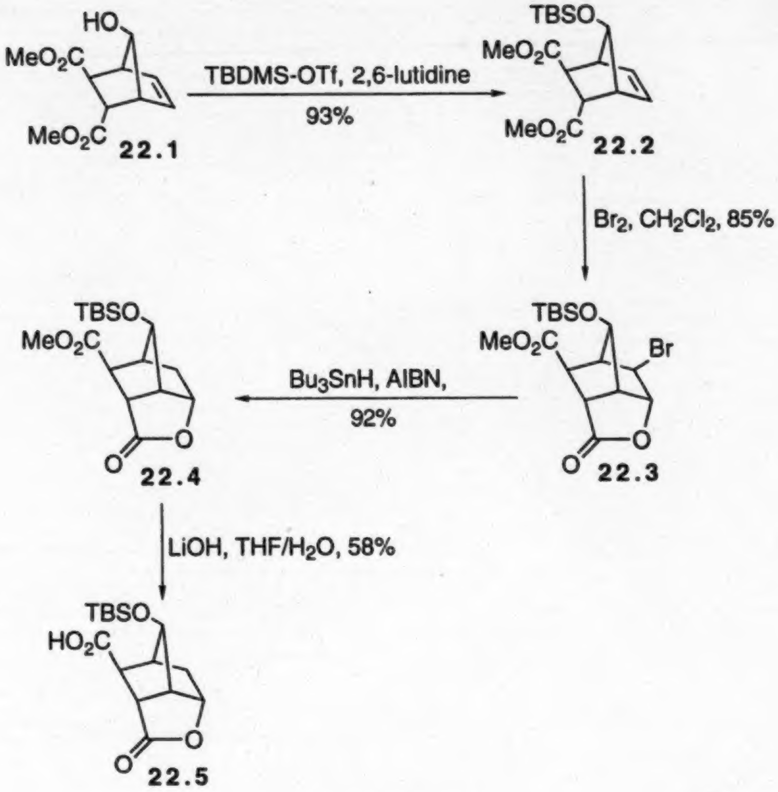


Scheme 21

(Scheme 21).

Retrosynthetic analysis of **21.1** indicates that it should be accessible by coupling tosylate **21.2** with the cuprate deriving from (*E*)-1-bromo-6-heptene.

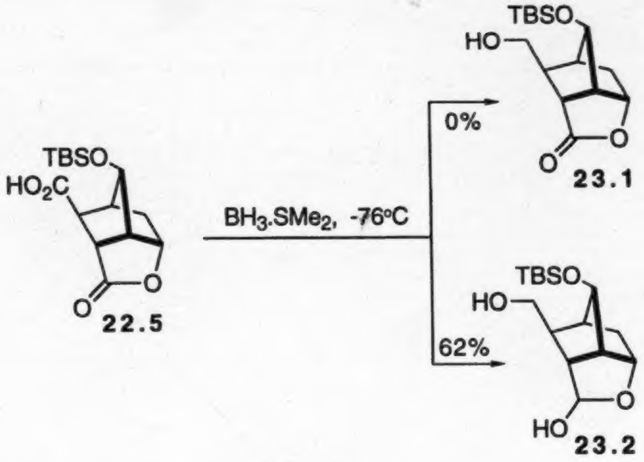
My first attempt to make **21.1** commenced with **22.1** (Scheme 22), which was readily prepared by the literature method.[11] Protection of the hydroxyl group of **22.1**, using *t*-$BuMe_2SiOSO_2CF_3$ and 2,6-lutidine, was followed by bromolactonization with Br_2. This procedure furnished **22.3**. The bromine atom was removed by stannane reduction, and hydrolysis of the resulting ester **22.4** with LiOH in THF-MeOH gave acid **22.5** after acidification.



Scheme 22

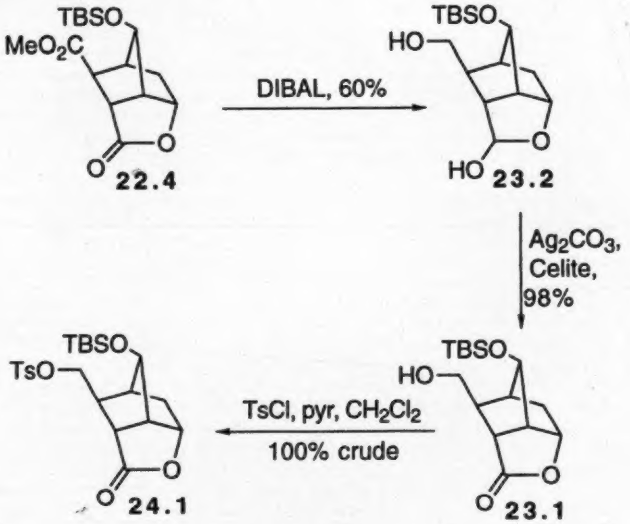
Unfortunately, $BH_3.SMe_2$ did not selectively reduce the acid functionality in **22.5** in the presence of lactone to give **23.1**, as we had expected, and only diol **23.2** (Scheme 23) was obtained (62%).

Because of this unexpected result we modified the route and proceeded as shown in Scheme 24. Reduction of lactone ester **22.4** with DIBAL gave rise to hydroxy lactol **23.2**, which were isolated in 62% yield. The lactol group was oxidized almost quantitatively to the lactone with Fétizon's



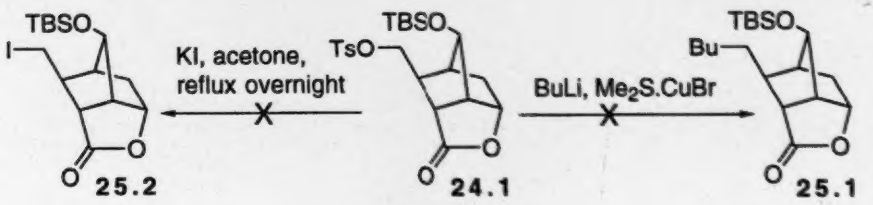
Scheme 23

reagent, giving **23.1**. Tosylation of **23.1** provided crude **24.1**, which was not stable to chromatography and thus was used directly for the next step.



Scheme 24

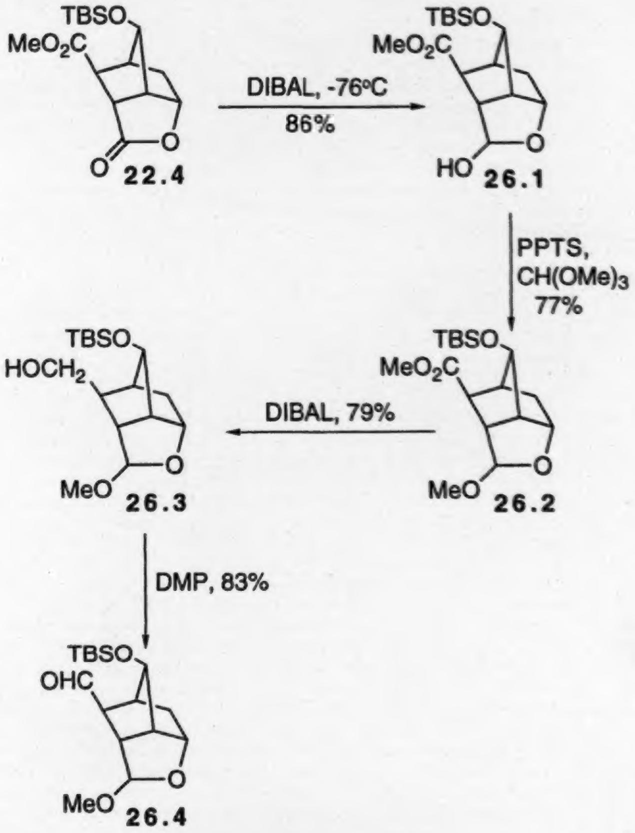
However, attempts to displace the tosylate group in **24.1** with a butyl group (from lithium dibutylcuprate) or with



Scheme 25

iodide were unsuccessful due to steric hindrance (Scheme 25).

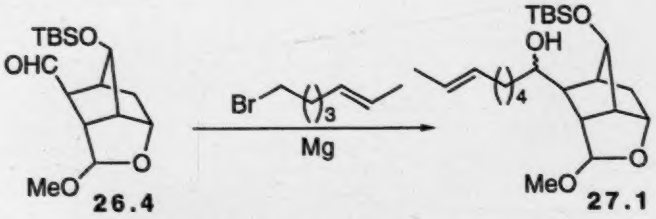
Consequently, we had to revise our route again, and in the new plan (Scheme 26) we aimed to make an aldehyde (for eventual reaction with a Grignard reagent). Selective reduction of lactone **22.4** with 3.2 equiv. DIBAL at -76 °C in



Scheme 26

CH_2Cl_2 afforded lactol **26.1** in 86% yield. Methylation of **26.1** upon treatment of PPTS and $CH(OMe)_3$ gave **26.2**. Reduction of **26.2** with DIBAL, followed by Dess-Martin oxidation of resultant alcohol, furnished aldehydes **26.4**. All the yields in this sequence are good.

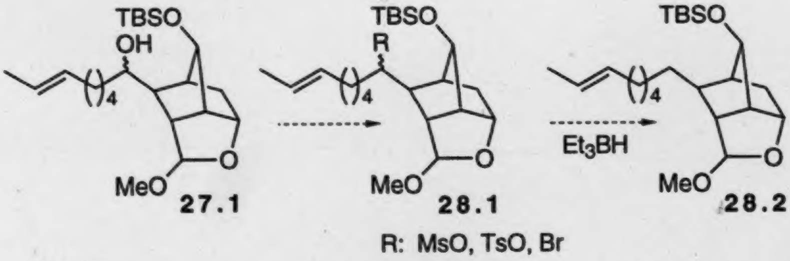
We then found that the efficacy of coupling of **26.4** with Grignard reagents to give **27.1** depended largely on the way the Grignard was prepared (Scheme 27). If the Grignard reagent was made by refluxing 1-bromo-6-heptene with Mg turnings in Et_2O, 6-8 equiv. of the bromide were needed to complete reaction and the yield was only 32-46%. However, if the Grignard reagent was made by addition of the bromide to a suspension of Rieke Mg (generated from $MgCl_2$ and K) in THF at 0 °C, coupling consumed only ca 3 equiv. of the bromide and the yield was 95%.



A. Mg turning, 6-8 eq. RBr, 32-46%,
B. Rieke Mg ($MgCl_2$ + K), 3 eq. RBr, 95%.

Scheme 27

Although alcohols **27.1** were obtained in high yield, deoxygenation of **27.1** presented formidable problems. We first planned to convert **27.1** into the corresponding mesylates, tosylates or bromides **28.1**, which when treated with $LiAlH_4$ or Super-hydride would give the deoxygenated products **28.2** (Scheme 28).

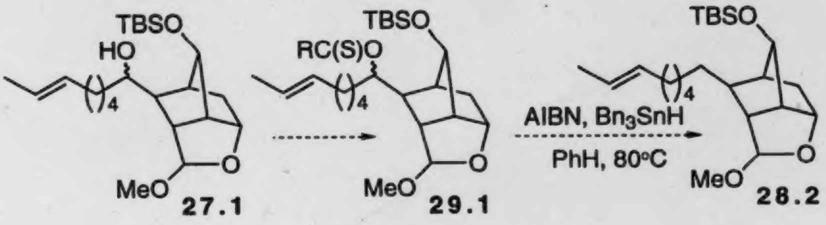


Scheme 28

Treatment of **27.1** with TsCl in the presence of DMAP did not effect tosylation, and only **27.1** was recovered. We attribute the lack of reactivity to steric hindrance. Mesylation of **27.1** (MsCl and pyridine) gave a crude mixture, which decomposed when treated with $LiAlH_4$ in refluxing THF. Reaction of **27.1** with Ph_3P and CBr_4 in THF led to a mixture of unidentified compounds.

Next, we turned to the Barton deoxygenation method (Scheme 29). According to our plan, **27.1** was converted into a variety of thiocarbonyl derivatives (**29.1**) which were then subjected to radical reduction conditions to afford deoxygenated compounds **28.2**.

Reaction of **27.1** with thiocarbonyl diimidazole (THF, refluxing overnight) did not give any of the desired compound, and only starting material was recovered. When **27.1** was treated sequentially with NaH, CS_2 and MeI, the



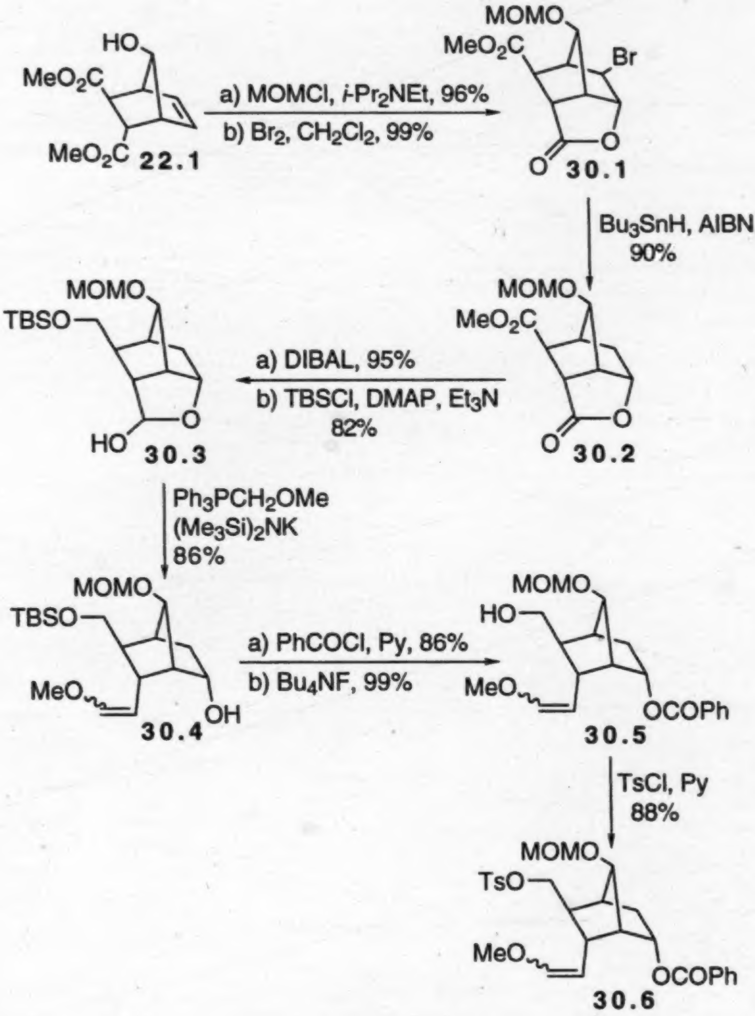
R: MeS, Im, *p*-FC_6H_4O

Scheme 29

xanthate (not very pure) was obtained in 66% yield (based on conversion). Radical reduction of the xanthate (AIBN, Bu_3SnH, benzene, reflux) provided **28.2** in 77% yield. However, the compound was not very pure and contained some *cis* olefin isomer resulting from reversible addition of stannane to the double bond. Reaction of **27.1** with 4-$FC_6H_4OC(=S)Cl$ in the presence of DMAP and pyridine in CH_2Cl_2 was completed overnight at room temperature. Radical reduction of the resulting crude thioester (AIBN, Bu_3SnH, benzene, reflux) gave **28.2**. Although overall yield of this method (59%) was good, a small amount of the *cis* olefin was formed and we were unable to remove it; hence we decided to abandon this route.

Meanwhile another member of this laboratory (Dr. Sun) studied alternative approaches, which also started with alcohol **22.1**. One of the routes examined is shown in Schemes 30 and 31.

Protection of **22.1** as a MOM ether was followed by bromolactonization, affording **30.1** (Scheme 30). Debromination of **30.1** under radical conditions gave lactone

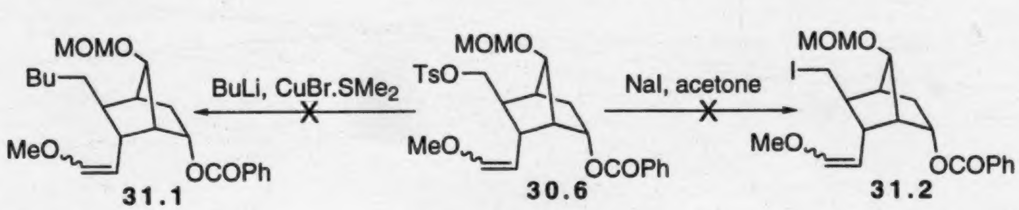


Scheme 30

30.2, and this was reduced to the corresponding lactol alcohol. The primary hydroxyl was then protected as its *t*-butyldimethylsilyl ether (**30.3**). Wittig reaction of **30.3** [Ph_3PCH_2OMe, $(Me_3Si)_2NK$, PhMe] provided **30.4**. Protection of the secondary hydroxyl as its benzoyl ester was followed by removal of the *t*-$BuMe_2Si$ group with Bu_4NF, giving rise to alcohol **30.5**. Upon treatment with TsCl and pyridine, **30.5**

was converted into tosylate **30.6**, and the stage was set to build up the C_8 sidechain.

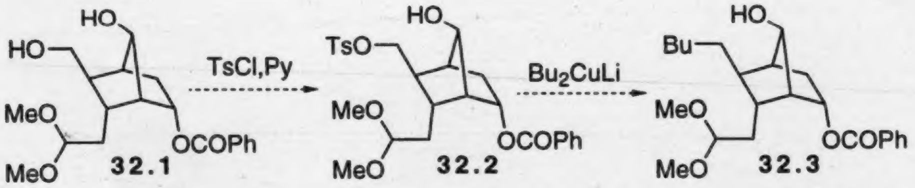
However, attempts to displace the tosylate group of **30.6** with a butyl group (from lithium dibutylcuprate) or an iodide were unsuccessful due to steric hindrance (Scheme 31).



Scheme 31

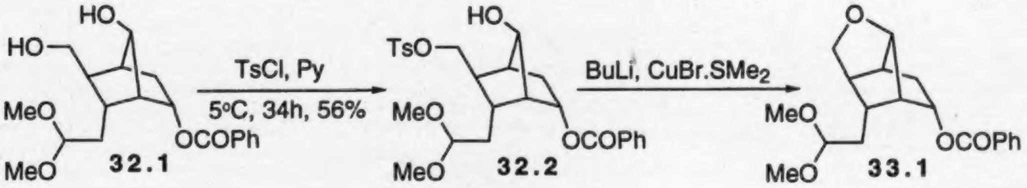
Although Dr. Sun did not succeed in attaching the sidechain onto the main skeleton, before he took up a position in a pharmaceutical company, he had also tried a couple of other routes and had made some quite advanced intermediates. I decided to use several of these (some of them being available in gram quantities) as the starting points for further attempts at installing the sidechain.

First, we planned to convert **32.1** into tosylate **32.2**, as coupling of **32.2** with dibutylcuprate should then give **32.3** (Scheme 32).



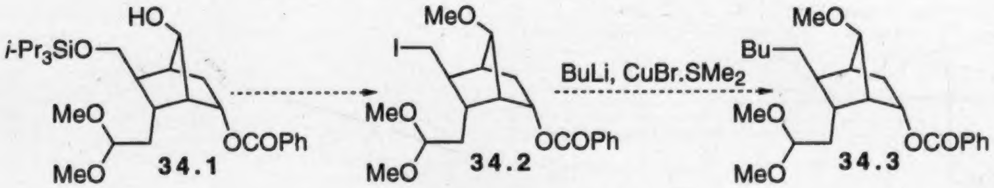
Scheme 32

Selective tosylation of the primary hydroxyl of **32.1** in the presence of the secondary hydroxyl gave **32.2** in 64% yield (based on conversion); none of the ditosylated compound was detected (Scheme 33). However, reaction of **32.2** with dibutylcuprate (used as a test reagent instead of the hexenyl reagent that is actually needed for CP-225,917) did not generate the desired homologated compound **32.3**, and only the cyclic ether **33.1** was obtained (54% yield).



Scheme 33

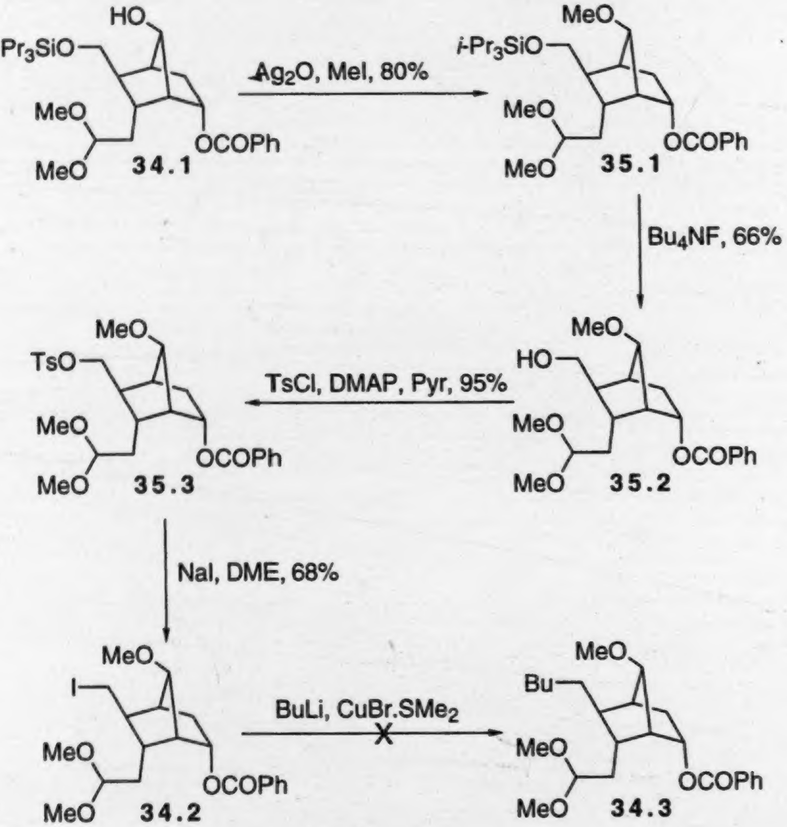
We next planned to convert **34.1** into iodide **34.2** in the expectation that reaction of **34.2** with dibutylcuprate would give the homologated product **34.3** (Scheme 34).



Scheme 34

O-Methylation of **34.1** using Ag_2O and MeI gave the corresponding methyl ether in 80% yield (Scheme 35). Cleavage of the silicon protecting group with Bu_4NF furnished

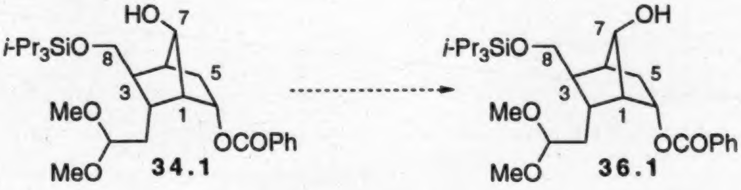
35.2 in 66% yield. Tosylation with TsCl, catalyzed by DMAP, afforded the tosylate in 95% yield, and replacement of the tosylate group with iodide gave **34.2** in 68% yield. However, due to steric hindrance, coupling of **34.2** with dibutylcuprate did not take place, and **34.2** was recovered unchanged.



Scheme 35

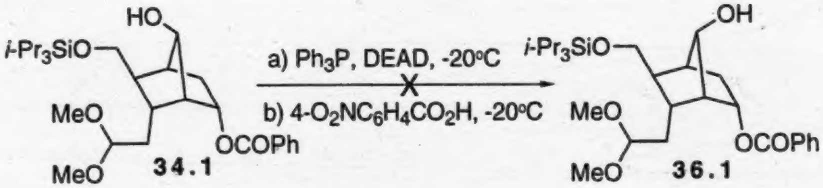
The failure of our attempts to attach a chain to the core structure , convinced us that it is not possible to overcome the steric hindrance that is due to the *syn* arrangement of the hydroxyl group at C-7 relative to C-8

(Scheme 36). We reasoned that it should be much easier to install the sidechain on the core structure if we could invert the stereochemistry at C-7 so that the oxygen function is *anti* to the C-8.



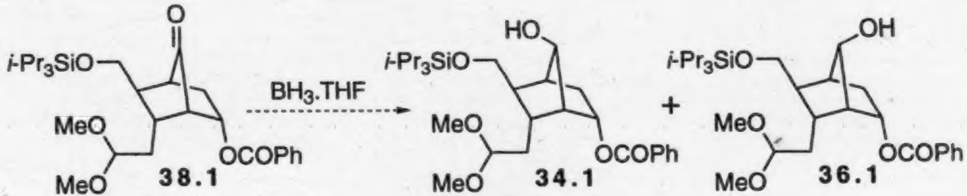
Scheme 36

The classic way to invert a hydroxyl group is by use of the Mitsunobu reaction. However, in the present case, Mitsunobu reaction of **34.1** (Ph_3P, DEAD, -20 °C, then 4-$NO_2C_6H_4CO_2H$, -20 °C) gave a mixture of unidentified products (Scheme 37).



Scheme 37

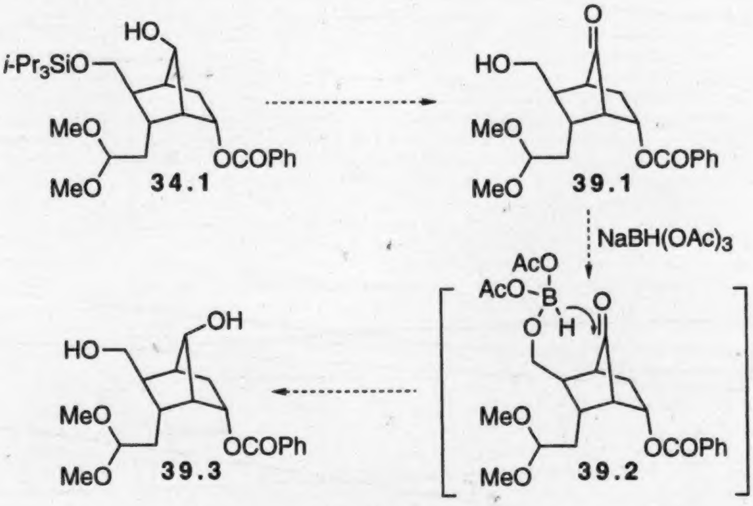
Next, we tried to reduce ketone **38.1** (which was also made by Dr. Sun) with BH_3.THF. Theoretically, we could get both **34.1** and **36.1**, but **34.1** could be recycled (Scheme 38). However, gentle refluxing of **38.1** with BH_3.THF in THF did not effect reduction of the ketone, and only starting material



Scheme 38

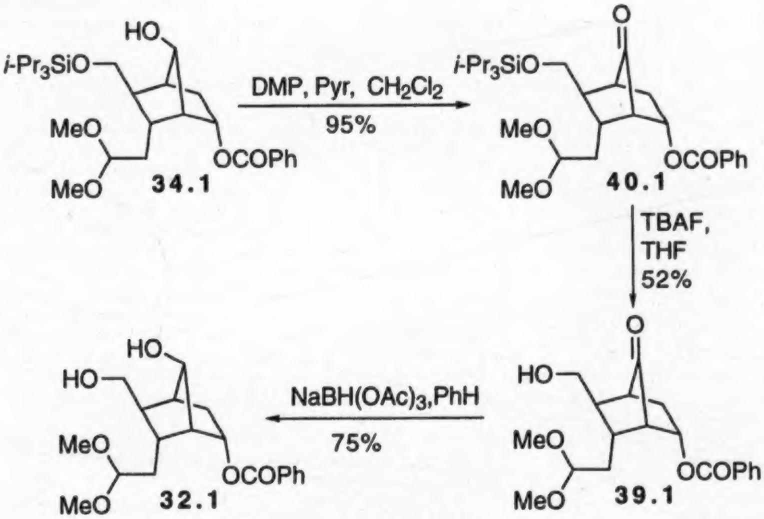
was recovered.

We also planned to convert **34.1** into **39.1** (Scheme 39), since reduction with NaBH(OAc)$_3$ would then generate **39.3** if complex **39.2** was formed first in the process.



Scheme 39

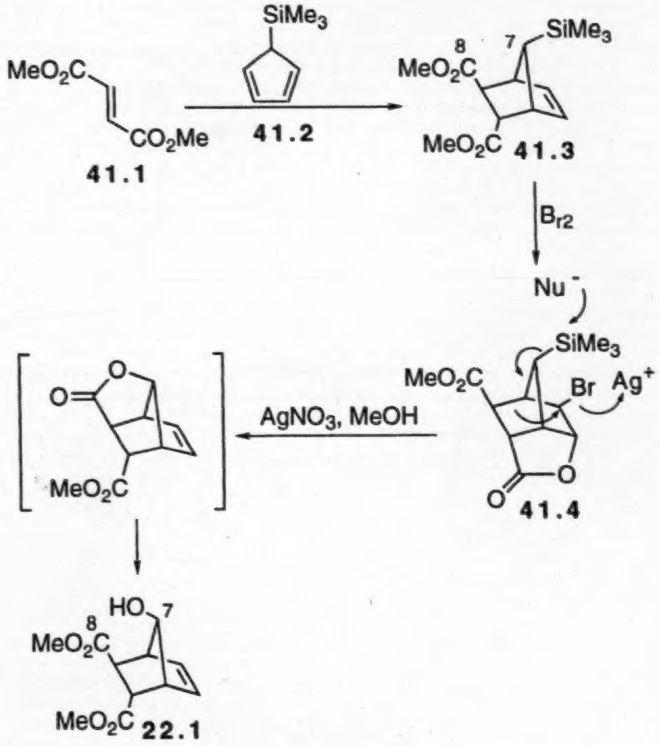
Oxidation of **34.1** with Dess-Martin periodinane in the presence of pyridine provided ketone **40.1** in high yield (Scheme 40), and deprotection with Bu$_4$NF gave the γ-hydroxy ketone **39.1** in moderate (52%) yield. It is possible that the acetal group in **40.1** is sensitive to trace amounts of water in the Bu$_4$NF solution, and this might account for the modest yield. Reduction of **39.1** with $NaBH(OAc)_3$ in PhH did not provide the expected **39.3**; only **32.1** was formed and in quite good yield (75%). Reduction of **39.1** with $NaBH(OAc)_3$ in AcOH gave **32.1** in 44% yield plus 14% of an unknown compound (which was not pure).



Scheme 40

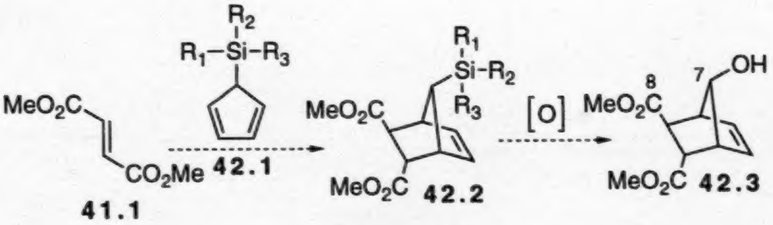
These unsuccessful experiments caused us to examine Fleming's paper[11] in which he described the synthesis of **41.3** from Diels-Alder reaction of dimethyl fumarate (**41.1**) with (trimethylsilyl)cyclopentadiene (**41.2**) (Scheme 41). In **41.3** the trimethylsilyl group at C-7 is *anti* to C-8.

I reasoned that if, instead of using (trimethylsilyl)-cyclopentadiene (**41.2**), we were to use a suitably substituted silycyclopentadiene (**42.1**) for reaction with dimethyl fumarate (**41.1**) (Scheme 42), then Tamao-Fleming oxidation of



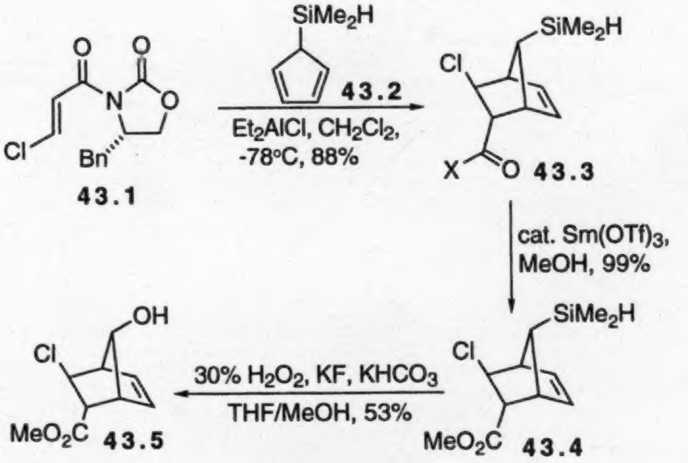
Scheme 41

the resulting adduct **42.2** would give alcohol **42.3** in which the hydroxyl group at C-7 is *anti* to C-8.



Scheme 42

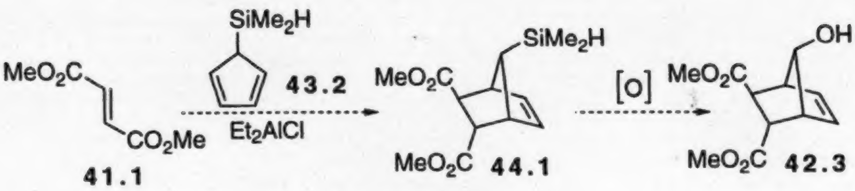
Examination of the literature, with this idea in mind, led us to Fukuyama's enantioselective total synthesis of (+)-gelsemine.[12] He used a Diels-Alder reaction between dienophile **43.1** and 5-(dimethylsilyl)cyclopentadiene (**43.2**) in the presence of Et_2AlCl. Reaction proceeded smoothly to provide adduct **43.3** (Scheme 43). After removal of the chiral auxiliary by treatment with $Sm(OTf)_3$ in MeOH, Tamao oxidation of the dimethylsilyl group of the resulting ester **43.4** with H_2O_2 in the presence of KF provided alcohol **43.4** in 53% yield.



Scheme 43

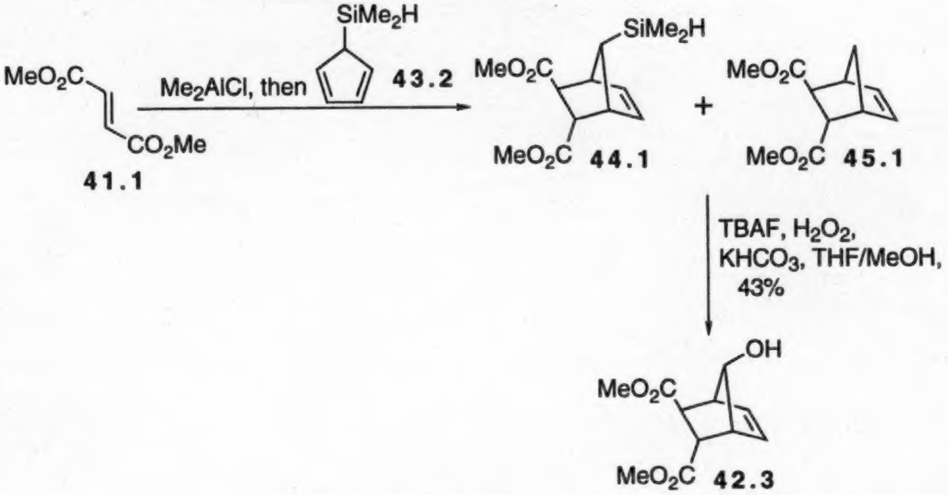
Based on Fukuyama's work, we expected reaction of dimethyl fumarate (**41.1**) with (dimethylsilyl)cyclopentadiene (**43.2**) in the presence of R_2AlCl would give adduct **44.1** (Scheme 44). Tamao oxidation would lead to the desired compound **42.3** with the hydroxyl group *anti* to the ester group.

However, to our surprise, the Me_2AlCl-catalyzed Diels-Alder reaction between dimethyl fumarate (**41.1**) with (dimethylsilyl)cyclopentadiene (**43.2**) gave a mixture of the



Scheme 44

desired **44.1** and the desilylated adduct **45.1** (Scheme 45). We think formation of **45.1** is due to the fact that **43.2** is not stable in the presence of Me_2AlCl and some of **43.2** releases a dimethlysilyl group to give cyclopentadiene; this reacts with dimethyl fumarate furnishing **45.1**.

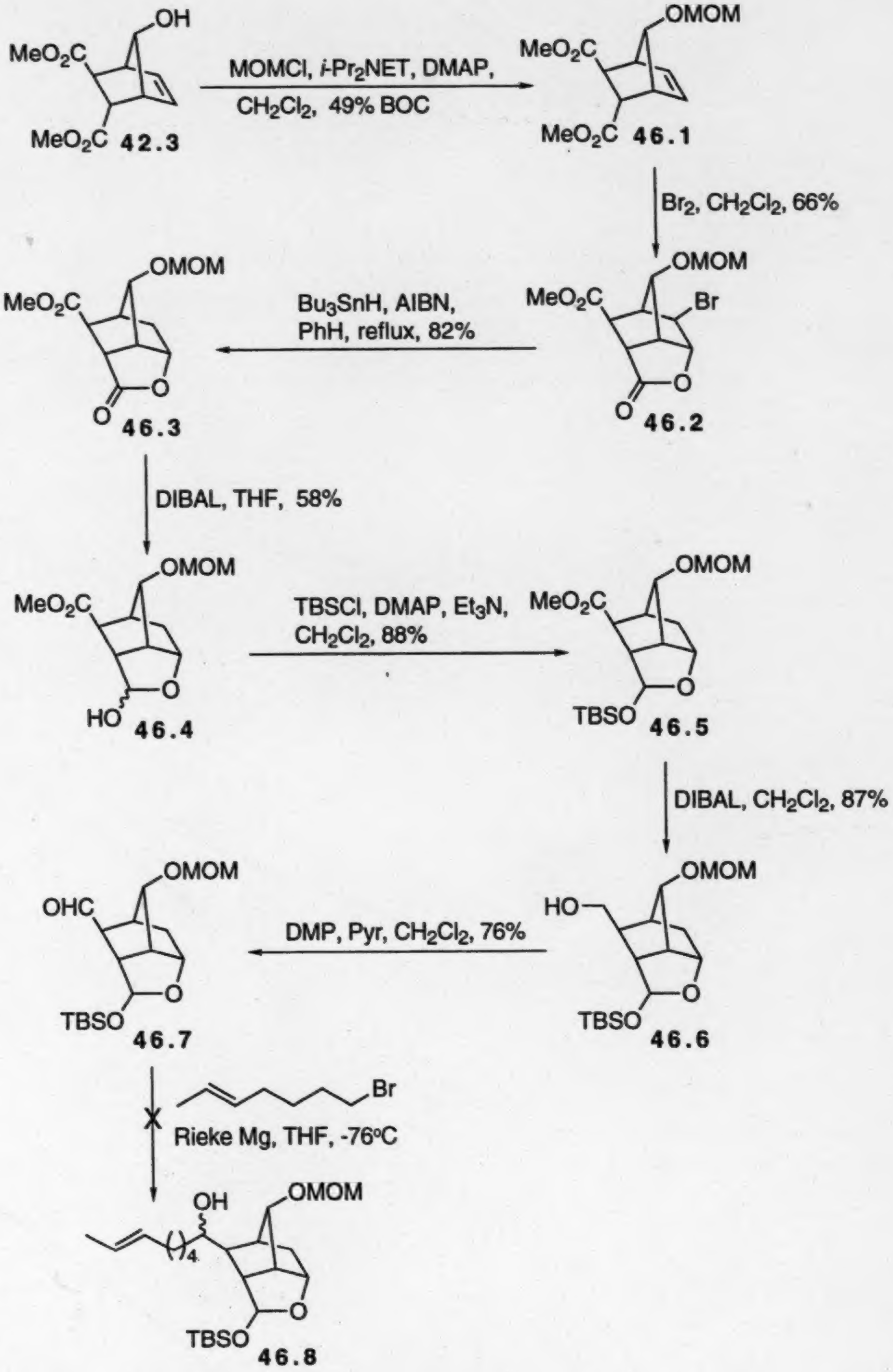


Scheme 45

Tamao oxidation of the mixture of **44.1** and **45.1** (Bu_4NF, H_2O_2, $KHCO_3$ in THF/MeOH), followed by chromatographic separation gave **42.3** in 43% yield. Although the yield is moderate, the compound can be made in only two steps, using cheap materials, and so we decided to continue with this route.

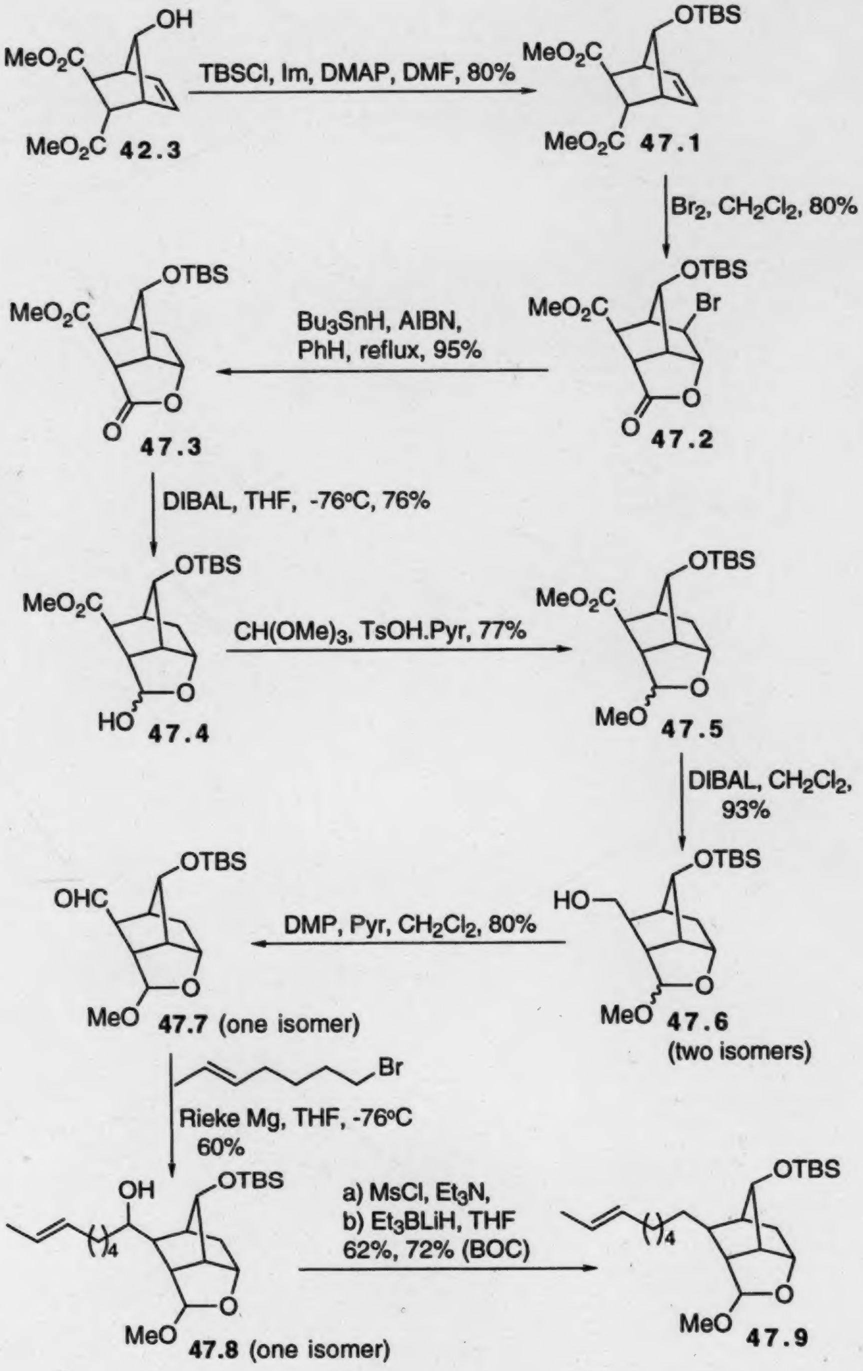
Two approaches towards installation of the seven carbon chain to the core structure were attempted. The first is shown in Scheme 46.

Reaction of **42.3** with MOMCl in the presence of *i*-Pr_2NEt and DMAP was slow and gave **46.1** in 49% yield (based on conversion) after two days. Bromination of **46.1** (Br_2, CH_2Cl_2) then provided the expected bromolactone, which was subjected to radical reduction conditions to give lactone **46.3**. Selective reduction of the lactone carbonyl of **46.3** in the presence of the ester, using DIBAL, generated the desired lactols in 58% yield, and reaction with *t*-$BuMe_2SiCl$ in the presence of DMAP and Et_3N gave rise to **46.5** in 88% yield. The ester group of **46.5** was reduced to the alcohol with DIBAL, and oxidation using the Dess-Martin periodinane in the presence of pyridine afforded aldehyde **46.7** in 76% yield. Unfortunately, coupling of **46.7** with heptenylmagnesium bromide did not give the desired **46.5**. Only a mixture of unknown compounds was obtained. We suspected that *t*-$BuMe_2Si$-protected lactol was labile to the Grignard reagent, and so we decided to convert the lactol into the *O*-methyl acetal, in the hope that the methyl acetal would be more resistant to attack by Grignard reagent than the siloxy acetal.


42.3
MOMCl, *i*-Pr$_2$NET, DMAP, CH$_2$Cl$_2$, 49% BOC
46.1
Br$_2$, CH$_2$Cl$_2$, 66%
46.2
Bu$_3$SnH, AIBN, PhH, reflux, 82%
46.3
DIBAL, THF, 58%
46.4
TBSCl, DMAP, Et$_3$N, CH$_2$Cl$_2$, 88%
46.5
DIBAL, CH$_2$Cl$_2$, 87%
46.6
DMP, Pyr, CH$_2$Cl$_2$, 76%
46.7
Rieke Mg, THF, -76°C
46.8

Scheme 46

The modified route based on above plan is outlined in



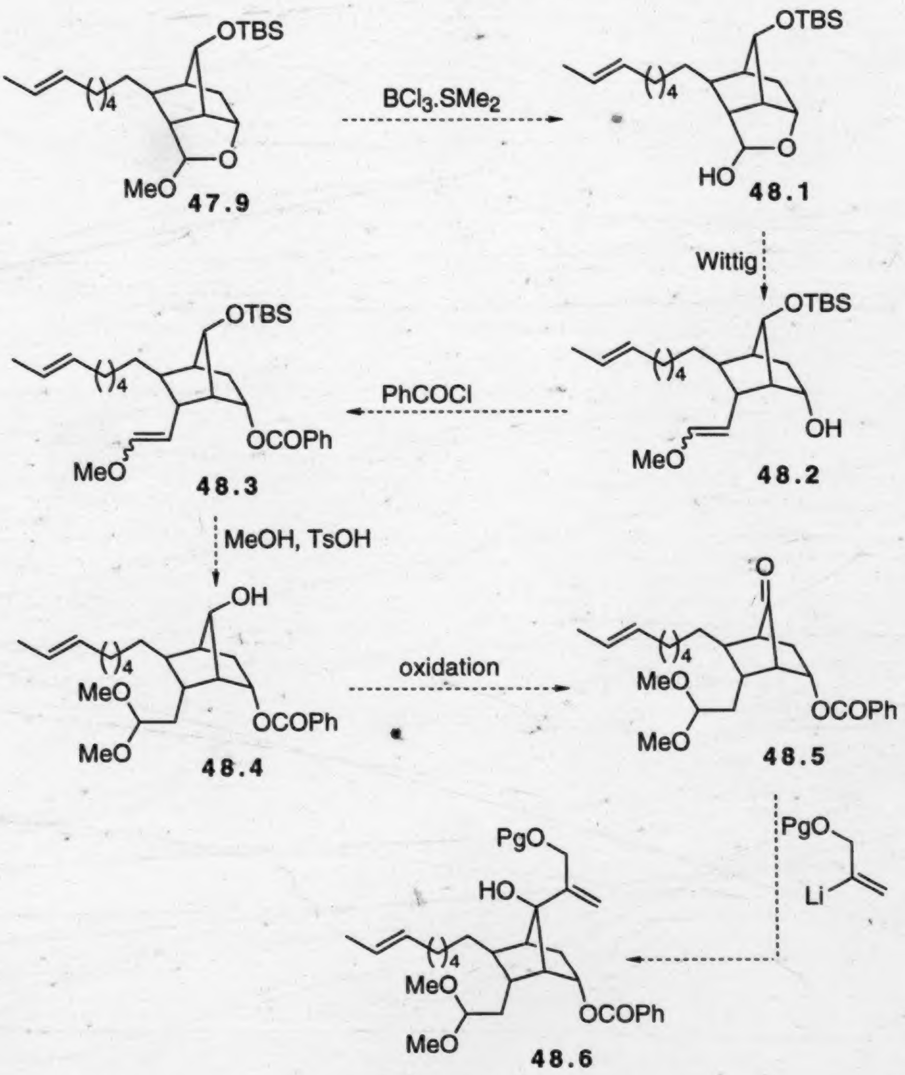
Scheme 47

Scheme 47.

Alcohol **42.3** was first protected as its *t*-butyldimethylsilyl ether using *t*-BuMe$_2$SiCl, imidazole and DMAP, to give **47.1** in 80% yield. Bromolactonization of **47.1** with Br$_2$ was followed by debromination of the resultant bromide, furnishing lactone **47.3** in 76% yield (two steps). Selective reduction of the lactone in **47.3** with ca 3 equiv DIBAL at -76 °C gave the lactols in 76% yield, and treatment with CH(OMe)$_3$ and PPTS led to methyl acetals **47.5**. Reduction of the ester in **47.5** with DIBAL gave alcohol **47.6** as two isomers. The yield of the major isomer was 79% and the yield of the minor was 14%. Oxidation of the major isomer with the Dess-Martin periodinane in the presence of pyridine afforded aldehyde **47.7** in yield 80%. The stereochemistry a the acetal carbon was not established. Coupling of **47.7** with heptenylmagnesium bromide (prepared from heptenyl bromide and Rieke magnesium) provided alcohol **47.8** in 60% yield, as a single isomer. Again, the stereochemistry at the newly-created asymmetric center was not determined. Mesylation of **47.8**, followed by treatment of the resulting mesylate with a large excess of Super-hydride in refluxing THF gave the homologated compound **47.9** in 62% yield.

Conclusion and further work

The results described above constitute a method for making a [2.2.1] bicyclic compound having one of the C$_8$ chains of CP-225,917, and the next tasks involve conversion of the lactol methyl ether **47.9** into the corresponding lactols (**47.9** → **48.1**) in order to set the stage for Wittig homologation (**48.1** → **48.2**), as summarized in Scheme 48. After appropriate functional group manipulation (**48.2** → **48.3** → **48.4** → **48.5**), our plan would be to attach a



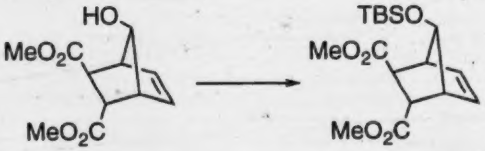
Scheme 48

three-carbon unit (**48.5** → **48.6**), and then try to build up the strained lactone unit, as in the model studies already published from this laboratory. Work to these ends is underway.

Experimental

Unless stated to the contrary, the general procedures used previously[13] in this laboratory were followed. The symbols s′, d′, t′, and q′ used for ^{13}C NMR signals indicate zero, one, two, or three attached hydrogens, respectively. Compounds were judged to be pure if they were homogeneous by TLC and gave high quality ^1H and ^{13}C NMR spectra free of impurity signals.

(2-*endo*, 3-*exo*, 7-*syn*)-7-(*tert*-Butyldimethylsilanyloxy)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic Acid Dimethyl Ester (22.2).

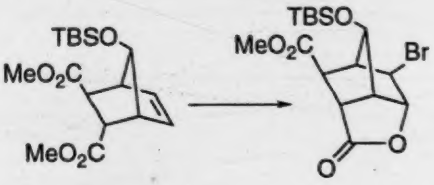


22.1 **22.2**

t-BuMe$_2$SiOTf (0.25 mL, 1.1 mmol) was added dropwise by syringe to a stirred and cooled (0 °C) solution of **22.1** (196 mg, 0.867 mmol) and 2,6-lutidine (0.20 mL, 1.7 mmol) in CH$_2$Cl$_2$ (3 mL). The cold bath was left in place but not recharged and stirring was continued for 24 h. The mixture was then washed with saturated aqueous NaHCO$_3$ (5 mL), 5% hydrochloric acid (10 mL), and brine (2 x 10 mL). The organic extract was dried (MgSO$_4$) and evaporated. Flash chromatography of the

residue over silica gel (2 x 10 cm), using 1:15 EtOAc-hexanes, gave **22.2** (266 mg, 90%) as an oil: FTIR (CH_2Cl_2 cast) 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ -0.02 (s, 3 H), 0.03 (s, 3 H), 0.82 (s, 9 H), 2.71 (d, J = 1.5 Hz, 1 H), 2.82-2.93 (m, 1 H), 3.03-3.12 (m, 1 H), 3.43-3.78 (m, 8 H), 5.82-5.91 (m, 1 H), 6.08-6.19 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ -5.2 (q'), -5.1 (q'), 17.8 (s'), 25.5 (q'), 44.7 (d'), 46.3 (d'), 50.4 (d'), 50.7 (d'), 51.6 (q'), 51.8 (q'), 84.3 (d'), 132.7 (d'), 135.5 (d'), 173.3 (s'), 174.6 (s'); exact mass *m/z* calcd for $C_{17}H_{28}O_5Si$ 340.17059, found 340.1705.

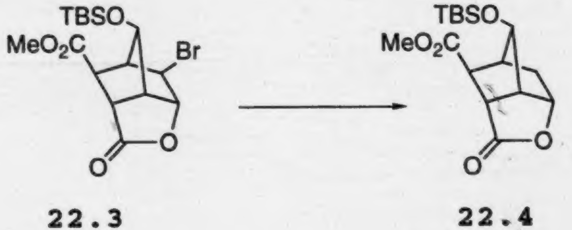
(2-*exo*, 9-*exo*, 8-*syn*)-2-Bromo-8-(*tert*-butyl-dimethylsilanyloxy)-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]-nonane-9-carboxylic Acid Methyl Ester (22.3).



22.2 **22.3**

A solution of Br_2 (1.90 mL, 36.8 mmol) in CH_2Cl_2 (20 mL) was added dropwise by additional funnel to a stirred and cooled (0 °C) solution of **22.2** (10.5 g, 30.9 mmol) in CH_2Cl_2 (100 mL). The ice bath was removed, stirring was continued for 4 h, and the reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$. The organic layer was washed with brine (2 x 100 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5.5 x 21 cm), using 3:40 EtOAc-hexanes, gave **22.3** (9.34 g, 75%) as a solid: mp 82-83 °C; FTIR (CH_2Cl_2 cast) 1742, 1796 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 3 H), 0.02 (s, 3 H), 0.79 (s, 9 H), 2.63 (s, 1 H), 3.03-3.05 (m, 1 H), 3.07 (s, 1 H), 3.42-3.44 (m, 1 H), 3.64 (s, 3 H), 3.75 (s, 1 H), 4.66 (s, 1 H), 4.75-4.76 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.06 (q'), -5.04 (q'), 18.1 (s'), 25.6 (q'), 40.3 (d' or q'), 49.1 (d' or q'), 49.3 (d' or q'), 51.0 (d' or q'), 52.5 (d' or q'), 53.2 (d' or q'), 77.6 (d'), 84.0 (d'), 169.5 (s'), 176.8 (s'); exact mass *m/z* calcd for $C_{16}H_{25}{}^{79}BrNaO_5Si$ 427.05523, found 427.0552.

(9-*exo*, 8-*syn*)-8-(*tert*-Butyldimethylsilanyloxy)-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-carboxylic Acid Methyl Ester (22.4).

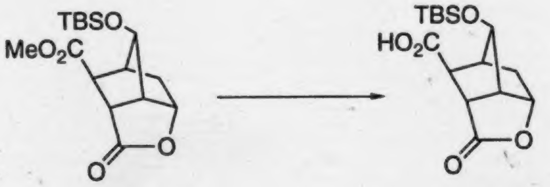


22.3 **22.4**

Bu_3SnH (7.50 mL, 27.9 mmol) and AIBN (453.1 mg, 2.76 mmol) were added to a solution of **22.3** (9.3051 g, 23.0 mmol) in PhH (75 mL), and the solution was refluxed for 2 h.

Evaporation of the solvent and flash chromatography of the residue over silica gel (5.5 x 16 cm), using 1:20 and then 1:4 EtOAc-hexanes, gave **22.4** (7.35 g, 98%) as a solid: mp 94-95 °C; FTIR (CH_2Cl_2 cast) 1738, 1778 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.81 (s, 9 H), 1.52 (d, J = 14.8 Hz, 1 H), 1.83-1.90 (m, 1 H), 2.63-2.67 (m, 1 H), 2.79-2.87 (m, 1 H), 2.97-3.03 (m, 1 H), 3.45-3.50 (m, 1 H), 3.67 (s, 3 H), 4.03-4.08 (m, 1 H), 4.61-4.65 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.1 (q′), -5.0 (q′), 18.1 (s′), 25.5 (q′), 34.6 (t′), 41.4 (d′), 45.0 (d′), 49.5 (d′), 51.6 (d′ or q′), 52.1 (d′ or q′), 77.0 (d′), 78.6 (d′), 171.1 (s′), 178.7 (s′); exact mass *m/z* calcd for $C_{16}H_{26}NaO_5Si$ 349.14472, found 349.1445.

(9-*exo*, 8-*syn*)-8-(*tert*-Butyldimethylsilanyloxy)-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-carboxylic Acid (22.5).

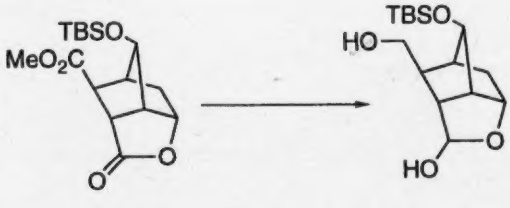


22.4 **22.5**

Lactone **22.4** (125.2 mg, 0.383 mmol) was added to a solution of 2 N NaOH (3.0 mL, 6.0 mmol) and EtOH (6 mL), and the mixture was heated in an oil bath (set at 62 °C) for 4 h.

The mixture was cooled to room temperature, acidified with 5% hydrochloric acid to pH <3 (pH paper) and extracted with Et_2O (2 x 25 mL). The combined organic extracts were washed with brine (2 x 30 mL), and dried ($MgSO_4$). Evaporation of the solvent gave **22.5** (69.2 mg, 58%) as a solid: mp 175-180 °C; FTIR (CH_2Cl_2 cast) 1699, 1777 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.05 (s, 3 H), 0.08 (s, 3 H), 0.84 (s, 9 H), 1.58 (d, J = 14.2 Hz, 1 H), 1.87-1.94 (m, 1 H), 2.66-2.72 (m, 1 H), 2.85-2.92 (m, 1 H), 3.02-3.07 (m, 1 H), 3.44-3.49 (m, 1 H), 4.09 (s, 1 H), 4.64-4.73 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.3 (q'), -5.1 (q'), 17.9 (s'), 25.5 (q'), 34.4 (t'), 41.2 (d'), 45.0 (d'), 49.3 (d'), 51.6 (d'), 77.0 (d'), 78.5 (d'), 177.6 (s'), 178.8 (s'); exact mass m/z calcd for $C_{15}H_{24}NaO_5Si$ 335.12907, found 335.1291.

(9-*exo*, 8-*syn*)-8-(*tert*-Butyldimethylsilanyloxy)-9-hydroxymethyl-4-oxatricyclo[4.2.1.0^{3,7}]nonan-5-ol (23.2).

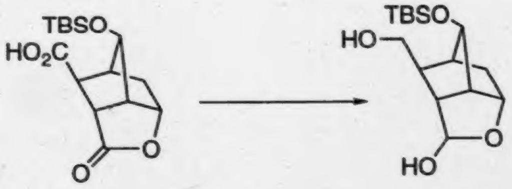


22.4 **23.2**

DIBAL (1 M in CH_2Cl_2, 9.50 mL, 9.50 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **22.4**

(616 mg, 1.89 mmol) in CH_2Cl_2. Stirring at -76 °C was continued for 8 h, and the reaction was then quenched by addition of MeOH (10 mL). The mixture was washed with 5% hydrochloric acid (20 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (30 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3.5 x 20 cm), using 1:100 to 1:25 MeOH-CH_2Cl_2, gave **23.2** (353 mg, 60%) as a solid: mp 139-142 °C; FTIR (CH_2Cl_2 cast) 3350 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.21 (s, 6 H), 0.98 (s, 9 H), 1.19 (d, J = 12.7 Hz, 1 H), 1.53-1.72 (m, 2 H), 1.98 (s, 1 H), 2.55-2.61 (m, 1 H), 2.81-2.92 (m 1 H), 3.06-3.61 (broad peak, -OH, 2 H), 3.69-3.76 (m, 2 H), 3.93 (s, 1 H), 4.34-4.42 (m, 1 H), 5.34 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.0 (q'), -4.8 (q'), 18.2 (s'), 25.8 (q'), 37.8 (t'), 43.5 (d'), 48.5 (d'), 48.6 (d'), 50.0 (d'), 65.1 (t'), 76.7 (d'), 79.4 (d'), 102.1 (d'); exact mass m/z calcd for $C_{15}H_{28}NaO_4Si$ 323.16546, found 323.1653.

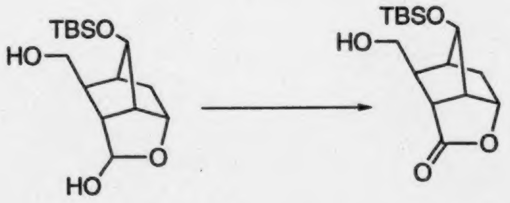
(9-*exo*, 8-*syn*)-8-(*tert*-Butyldimethylsilanyloxy)-9-hydroxymethyl-4-oxatricyclo[4.2.1.0^{3,7}]nonan-5-ol (23.2).



22.4 **23.2**

$BH_3.Me_2S$ (10 M in THF, 70 µL, 0.70 mmol) was added to a stirred and cooled (-78 °C) solution of **22.4** in THF (2 mL). The cold bath was left in place but not recharged and stirring was continued overnight, the mixture attaining room temperature over the course of 4 h. The mixture was quenched by addition of MeOH (1 mL), and then evaporated. Flash chromatography of the residue over silica gel (3.5 x 20 cm), using 1:5 to 1:1 EtOAc-hexanes, gave **23.2** (38.2 mg, 62%).

(9-*exo*, 8-*syn*)-8-(*tert*-Butyldimethylsilanyloxy)-9-hydroxymethyl-4-oxatricyclo[$4.2.1.0^{3,7}$]nonan-5-one (23.1).

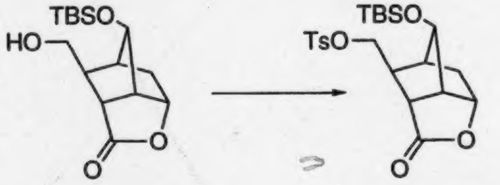


23.2 **23.1**

Ag_2CO_3-Celite[14] (726 mg, 1.24 mmol) was added to a solution of **23.2** (51 mg, 0.17 mmol) in PhH (29 mL) and the mixture was refluxed for 1 h and then filtered through a pad of Celite (3 x 2 cm). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 10 cm), using 1:5 EtOAc-hexanes, gave **23.1** (50 mg, 98%) as an oil: FTIR (CH_2Cl_2 cast) 1779, 3419 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.07 (s, 6 H), 0.86 (s, 9 H), 1.04 (d, J = 14.5 Hz, 1 H),

1.81-1.91 (m, 1 H), 2.16-2.22 (m, 1 H), 2.28 (s, 1 H), 3.61-3.71 (broad peak, -OH, 1 H), 2.72-2.76 (m, 1 H), 2.98-3.07 (m, 1 H), 3.76-3.88 (m, 2 H), 4.06 (s, 1 H), 4.63-4.68 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.1 (q'), 18.0 (s'), 25.7 (q'), 36.1 (t'), 42.6 (d'), 44.6 (d'), 50.9 (d'), 51.7 (d'), 64.8 (t'), 77.1 (d'), 79.4 (d'), 180.1 (s'); exact mass *m/z* calcd for $C_{15}H_{26}NaO_4Si$ 321.14981, found 321.1496.

Toluene-4-sulfonic Acid [(9-*exo*, 8-*syn*)-8-(*tert*-butyldimethylsilanyloxy)-4-oxa-5-oxotricyclo-[4.2.1.0^{3,7}]non-9-yl]methyl Ester (24.1).

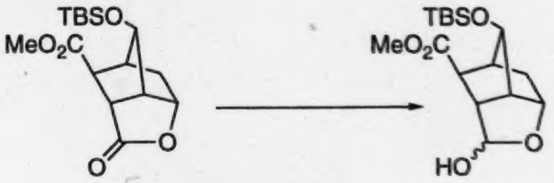


23.1 **24.1**

TsCl (172 mg, 0.902 mmol) was added to a stirred solution of **23.1** (150 mg, 0.463 mmol) and pyridine (0.60 mL, 7.4 mmol) in CH_2Cl_2 (6.0 mL). Stirring was continued overnight, and the mixture was then washed with 5% H_2SO_4 (15 mL) and brine (2 x 25 mL), and dried ($MgSO_4$). Evaporation of the solvent gave crude **24.1** (221 mg, 100%) as an oil: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 0.06 (s, 6 H), 1.85 (s, 9 H), 1.47 (d, J = 14.4 Hz, 1 H), 1.80-1.85 (m, 1 H), 2.26-2.34 (m, 2 H), 2.44-2.53 (m, 3 H), 2.96-3.02 (m, 1 H), 4.07 (s, 1 H), 4.16-4.27

(m, 1 H), 4.34-4.40 (m, 1 H), 4.61-4.66 (m, 1 H), 7.37 (d, *J* = 10.9 Hz, 2 H), 7.76 (d, *J* = 10.9 Hz, 3 H). The material is unstable and was used directly in the next step.

(9-*exo*, 8-*syn*)-8-(*tert*-Butyldimethylsilanyloxy)-5-hydroxy-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-carboxylic Acid Methyl Ester (26.1).

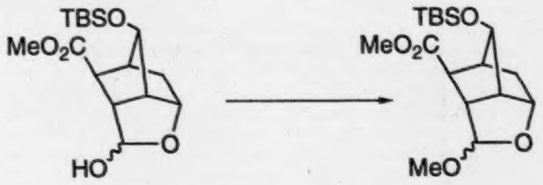


22.4 **26.1**

DIBAL (1 M in CH_2Cl_2, 33 mL, 33 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **22.4** (7.35 g, 22.5 mmol) in THF (100 mL). Stirring at -76 °C was continued for 2.5 h, and a further portion of DIBAL (1 M in CH_2Cl_2, 22 mL, 22 mmol) was added dropwise. The mixture was stirred at -76 °C for 3 h and quenched at -76 °C by addition of MeOH (25 mL). The mixture was acidified with 5% hydrochloric acid to pH 5 (pH paper), and extracted with EtOAc (1 x 150, 1 x 75 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5.5 x 17 cm), using 1:10 EtOAc-hexanes, gave **26.1** (7.18 g, 97%) as a mixture of two isomers: mp 75-78 °C;

FTIR (CH_2Cl_2 cast) 1736, 3407 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) (major isomer) δ -0.03 (s, 3 H), -0.01 (s, 3 H), 0.87 (s, 9 H), 1.04 (d, J = 14.0 Hz, 1 H), 1.13-1.19 (m, 1 H), 2.02-2.05 (m, 1 H), 2.51-2.54 (m, 1 H), 2.86-2.92 (m, 1 H), 3.40-3.49 (m, 4 H), 3.67-3.70 (m, 1 H), 4.04-4.09 (m, 1 H), 4.13-4.19 (m, 1 H), 5.28-5.33 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major isomer) δ -4.9 (q′), -4.7 (q′), 18.3 (s′), 26.0 (q′), 36.5 (t′), 43.6 (d′), 48.7 (d′), 48.9 (d′ or q′), 50.5 (d′ or q′), 51.4 (d′ or q′), 76.8 (d′), 79.2 (d′), 102.0 (d′), 173.1 (s′); exact mass *m/z* calcd for $C_{16}H_{28}NaO_5Si$ 351.16037, found 3351.1600.

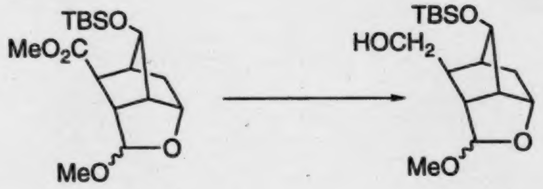
(9-*exo*, 8-*syn*)-8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-carboxylic Acid Methyl Ester (26.2).



26.1 **26.2**

TsOH.pyridine (77.4 mg, 0.31 mmol) was added to a solution of **26.1** (7.08 g, 21.6 mmol) in $CH(OMe)_3$ (60 mL). The resulting solution was stirred at room temperature overnight, diluted with Et_2O (200 mL), and washed with saturated aqueous $NaHCO_3$ (2 x 100 mL) and brine (2 x 100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (6 x 17 cm), using 1:20 EtOAc-hexanes, gave **26.2** (5.69 g, 77%) as a mixture of two isomers: 47-49 °C; FTIR (CH_2Cl_2 cast) 1738 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ -0.05 (s, 6 H), 0.85 (s, 9 H), 1.06 (d, J = 13.2 Hz, 1 H), 1.14-1.20 (m, 1 H), 2.03-2.07 (m, 1 H), 2.52-2.56 (m, 1 H), 2.77-2.80 (m, 1 H), 3.18 (s, 3 H), 3.42-3.47 (m, 4 H), 3.66-3.69 (m, 1 H), 4.03-4.08 (m, 1 H), 4.66 (s, 1 H); ^{13}C NMR (C_6D_6, 100 MHz) δ -5.1 (q'), -4.9 (q'), 18.1 (s'), 25.8 (q'), 36.6 (t'), 43.5 (d'), 47.6 (d'), 48.8 (d'), 50.8 (d' or q'), 51.3 (d' or q'), 54.4 (q'), 76.8 (d'), 79.2 (d'), 108.4 (d'), 173.0 (s'); exact mass *m/z* calcd for $C_{17}H_{30}O_5Si$ 342.18625, found 342.1855.

[(9-*exo*, 8-*syn*)-8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{3,7}]non-9-yl]methanol (26.3).

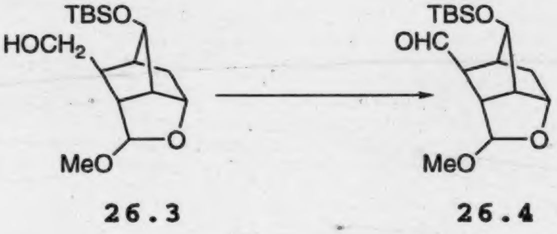


26.2 **26.3**

DIBAL (1 M in CH_2Cl_2, 5.5 mL, 5.5 mmol) was added to a stirred and cooled (-78 °C) solution of **26.2** (mixture of isomers) (543 mg, 1.59 mmol) in CH_2Cl_2 (30 mL). The cold bath was left in place, but not recharged, and stirring was continued overnight. The mixture was recooled to -78 °C and water (10 mL) was added. The mixture was filtered through a pad of Celite (5 x 3 cm) and the pad was washed with EtOAc (150 mL). The organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 13 cm), using 1:20 to 1:3 EtOAc-hexanes, gave **26.3** as two separate isomers, which were obtained as oils: minor isomer A (38 mg, 7.6%), major isomer B (357 mg, 71.5%). Minor isomer A had: FTIR (CH_2Cl_2 cast) 3446 cm^{-1}; ^1H NMR (C_6D_6, 200 MHz) δ 0.04 (s, 6 H), 0.97 (s, 9 H), 1.28-1.37 (m, 2 H), 1.84-1.94 (m, 1 H), 2.06-2.13 (m, 1 H), 2.39-2.48 (m, 1 H), 2.57-2.68 (m, 2 H), 3.38 (s, 3 H), 3.58-3.67 (m, 1 H), 3.87-4.08 (m, 3 H), 4.94 (d, J = 4.2 Hz, 1 H); ^{13}C NMR (C_6D_6, 50 MHz) δ -5.1 (q′), -5.0 (q′), 18.2 (s′), 25.9 (q′), 38.4 (t′), 42.4 (d′), 44.8 (d′), 45.7 (d′), 52.4 (d′), 56.7 (q′), 65.7 (t′), 75.9 (d′), 79.6 (d′), 107.5 (d′); exact mass m/z calcd for $C_{16}H_{30}NaO_4Si$ 337.18111, found 337.1811.

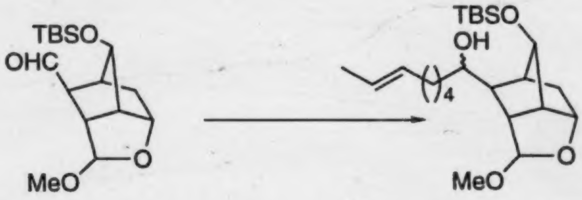
Major isomer B had: FTIR (CH_2Cl_2 cast) 3430 cm^{-1}; ^1H NMR (C_6D_6, 200 MHz) δ 0.03 (s, 6 H), 0.94 (s, 9 H), 1.17-1.33 (m, 2 H), 1.52-1.90 (m, 3 H), 2.73-2.79 (m, 1 H), 2.89-2.98 (m, 1 H), 3.33 (s, 3 H), 3.72-3.82 (m, 3 H), 4.21 (d, J = 5.2 Hz, 1 H), 4.87 (s, 1 H); ^{13}C NMR (C_6D_6, 75 MHz) δ -5.1 (q′), -4.9 (q′), 17.9 (s′), 25.9 (q′), 38.1 (t′), 43.2 (d′), 48.5 (d′), 49.1 (d′), 50.6 (d′), 54.4 (q′), 65.5 (t′), 76.8 (d′), 80.0 (d′), 109.0 (d′); exact mass m/z calcd for $C_{16}H_{30}NaO_4Si$ 337.18111, found 337.1812.

(9-*exo*, 8-*syn*)-8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-carbaldehyde (26.4).



Dess-Martin periodinane (3.654 g, 4.46 mmol)[15] was added to a stirred solution of **26.3** (major isomer)(1.40 g, 4.46 mmol) and pyridine (4.80 mL, 59.3 mmol) in CH_2Cl_2. Stirring was continued overnight and the mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ (50 mL) and 10% aqueous $NaHCO_3$ (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (5 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (4.5 x 14 cm), using 1:7 EtOAc-hexanes, gave **26.4** (1.184 g, 85%) as a solid: mp 113-115 °C; FTIR (CH_2Cl_2 cast) 1724 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ -0.10 (s, 3 H), -0.09 (s, 3 H), 0.83 (s, 9 H), 1.02 (d, *J* = 13.2 Hz, 1 H), 1.11-1.16 (m, 1 H), 1.64-1.67 (m, 1 H), 2.17-2.22 (m, 1 H), 2.73-2.77 (m, 1 H), 3.07-3.09 (m, 1 H), 3.19 (s, 3 H), 3.56-3.58 (m, 1 H), 4.03-4.06 (m, 1 H), 4.54 (s, 1 H), 9.48 (s, 1 H); ^{13}C NMR (C_6D_6, 100 MHz) δ -4.9 (q′), -4.7 (q′), 18.3 (s′), 26.0 (q′), 36.5 (t′), 44.4 (d′), 46.2 (d′), 50.9 (d′), 54.5 (d′), 55.6 (q′), 77.2 (d′), 79.0 (d′), 108.2 (d′), 201.3 (d′); exact mass *m/z* calcd for $C_{16}H_{28}O_4Si$ 312.17569, found 312.1752.

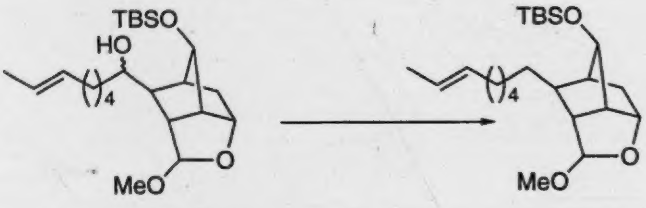
(*E*)-1-[(9-*exo*, 8-*syn*)-8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{3,7}]non-9-yl]oct-6-en-1-ol (27.1).



26.4 **27.1**

Rieke Mg[16] was prepared as follows: THF (55 mL) was added to a N_2-filled flask containing K (1.5191 g, 38.85 mmol) and $MgCl_2$ (2.1251 g, 22.3 mmol) and the mixture was stirred and refluxed for 2 h and then allowed to cool to room temperature for 40 min (stirring). (*E*)-1-Bromo-6-heptene[17] (1.901 g, 10.7 mmol) was added dropwise by syringe to the above suspension at 0 °C. Stirring was continued for 50 min at 0 °C. The resulting solution was cooled to -78 °C and the solids were allowed to settle. This cooled solution was transferred by cannula (N_2 pressure) to a stirred and cooled (-76 °C) solution of **26.4** (two isomers) (1.1287 g, 3.16 mmol) in THF (30 mL). The cold bath was left in place, but not recharged, and stirring was continued overnight. [Our impression is that the reaction takes less than 2 h at -78 °C.] The mixture was quenched by addition of saturated aqueous NH_4Cl to lower the pH to pH 7 (pH paper), and then filtered through a pad of Celite (8 x 1 cm). The pad was washed with EtOAc (100 mL). The organic filtrate was washed with brine (2 x 60 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (4.5 x 20 cm), using 1:40 to 1:8 EtOAc-hexanes, gave **27.1** as an oily mixture of two isomers (1.404 g, 97%): FTIR (CH_2Cl_2 cast) 3435 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ -0.03-0.02 (m, 6 H), 0.82-0.92 (m, 9 H), 1.12-1.79 (m, 13 H), 1.99-2.04 (m, 2 H), 2.23 (s 0.56 H), 2.36-2.37 (m, 0.53 H), 2.65-2.70 (m, 0.46 H), 2.85-2.90 (m, 0.80 H), 3.06-3.10 (m, 0.30 H), 3.25-3.37 (m, 3 H), 3.65-3.72 (m, 1 H), 3.80-3.90 (m, 1 H), 4.05-4.20 (m, 1 H), 4.80 (s, 0.52 H), 4.90 (s, 0.36 H), 5.37-5.48 (m, 2 H); ^{13}C NMR (C_6D_6, 125 MHz) δ -4.8 (q′), 18.1 (q′), 18.3 (s′), 25.9 (q′), 26.1 (t′), 30.0 (t′), 30.2 (t′), 33.1 (t′), 36.8 (t′), 37.2 (t′), 38.3 (t′), 38.6 (t′), 41.1 (d′), 45.3 (d′), 46.6 (d′), 49.2 (d′), 51.0 (d′), 53.0 (d′), 53.1 (d′), 54.4 (q′), 54.5 (q′), 72.7 (d′), 73.0 (d′), 76.8 (d′), 77.0 (d′), 80.0 (d′), 109.0 (d′), 109.6 (d′), 124.8 (d′), 124.9 (d′), 131.9 (d′), 132.0 (d′); exact mass *m/z* calcd for $C_{23}H_{42}NaO_4Si$ 433.27446, found 433.2748.

***tert*-Butyl-[(9-*exo*, 8-*syn*)-5-methoxy-9-[(*E*)-oct-6-enyl]-4-oxatricyclo[4.2.1.0^{3,7}]non-8-yloxy]dimethylsilane (28.2).**

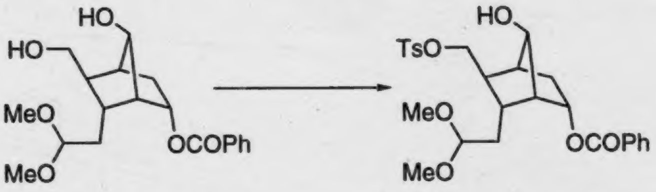


27.1 **28.2**

4-Fluorophenyl chlorothionoformate [4-$FC_6H_4OC(S)Cl$] (1.47 mL, 5.69 mmol) was added dropwise to a stirred solution of **27.1** (1.444 g, 3.52 mmol), DMAP (59.9 mg, 0.49 mmol) and pyridine (5.10 mL, 63.1 mmol) in CH_2Cl_2 (40 mL) at 15 °C (water bath). The water bath was removed and stirring was continued overnight. The mixture was evaporated and the residue was taken up in EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 100 mL) and brine (2 x 100 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 23 cm), using 1:100 to 1:10 EtOAc-hexanes, gave the crude thionocarbonate (1.799 g, 90%).

A solution of AIBN (55.2 mg, 0.337 mmol) in PhH (3 mL) was added over 3 h (syringe pump) to a refluxing solution of the crude thionocarbonate (1.691 g, ca 3.00 mmol) and Bu_3SnH (3.40 mL, 12.6 mmol) in PhH (14 mL). Refluxing was continued for 30 min after the addition. Evaporation of the solvent and flash chromatography of the residue over silica gel (4.5 x 20 cm), using 1:40 to 1:8 EtOAc-hexanes, gave **28.2** (containing some *Z*-isomer, <1:1) (812 mg, 59%) as an oil: ^1H NMR (C_6D_6, 400 MHz) δ -0.02 (s, 6 H), 0.91 (s, 9 H), 1.14 (d, *J* = 13.2 Hz, 1 H), 1.20-1.39 (m, 8 H), 1.53-1.70 (m, 6 H), 1.93-2.08 (m, 2 H), 2.51-2.53 (m, 1 H), 2.83-2.87 (m, 1 H), 3.26 (s, 3 H), 3.74 (s, 1 H), 4.15-4.19 (m, 1 H) 4.80 (s, 1 H), 5.36-5.51 (m, 2 H); ^{13}C NMR (C_6D_6, 100 MHz) δ -5.0 (q′), -4.9 (q′), 12.8 (q′), 18.0 (q′), 18.2 (s′), 26.0 (q′), 27.2 (t′), 28.67 (t′), 28.72 (t′), 29.6 (t′), 29.8 (t′), 29.9 (t′), 33.0 (t′), 35.65 (t′), 35.67 (t′), 38.4 (t′), 44.43 (d′), 44.46 (d′), 46.7 (d′), 51.0 (d′), 52.0 (d′), 54.3 (q′), 76.8 (d′), 80.4 (d′), 109.1 (d′), 123.8 (d′), 124.8 (d′), 131.0 (d′), 131.8 (d′); exact mass *m/z* calcd for $C_{23}H_{42}NaO_3Si$ 417.28009, found 417.2802.

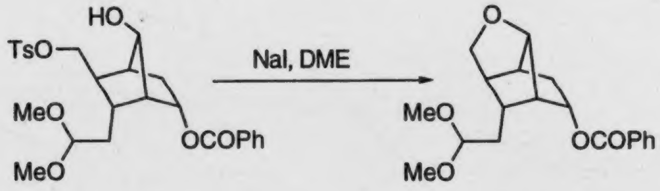
Benzoic Acid (*endo*-2, *exo*-5, *endo*-6, *anti*-7)-6-[(2,2-Dimethoxyethyl]-7-hydroxy-5-(toluene-4-sufonyl-oxymethyl)bicyclo[2.2.1]hept-2-yl Ester (32.2).



32.1 **32.2**

TsCl (40.3 mg, 0.211 mmol) was added to a stirred and cooled (5 °C) solution of **32.1** (73.7 mg, 0.211 mmol) in pyridine (0.5 mL) and CH_2Cl_2 (0.5 mL). Stirring at 5 °C was continued for 34 h. The mixture was diluted with brine (15 mL) and extracted with Et_2O (25 mL). The organic extract was washed with saturated aqueous $CuSO_4$ (10 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 9 cm), using 1:1 to 3:1 EtOAc-hexanes, gave **32.1** (10 mg) and **32.2** (59 mg, 56% or 64% based on conversion) as an oil: FTIR (CH_2Cl_2 cast) 1717 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 0.91-0.97 (m, 1 H), 1.45-1.57 (m, 1 H), 1.66-1.79 (m, 1 H), 1.82-2.32 (m, 7 H), 2.34-2.48 (m, 2 H), 3.03 (s, 3 H), 3.07 (s, 3 H), 3.42 (s, 1 H), 4.33-4.52 (m, 3 H), 5.06-5.18 (m, 1 H), 6.72 (d, *J* = 8.1 Hz, 2 H), 7.05-7.19 (m, 3 H), 7.80 (d, *J* = 8.1 Hz, 2 H), 8.07-8.19 (m, 2 H); ^{13}C NMR (C_6D_6, 100 MHz) δ 21.1 (q'), 35.2 (t'), 36.1 (t'), 36.8 (d'), 43.3 (d'), 48.9 (d'), 49.2 (d'), 51.3 (q'), 52.3 (q'), 74.2 (d'), 74.3 (t'), 77.7 (d'), 103.7 (d'), 128.6 (d'), 129.8 (d'), 129.9 (d'), 130.8 (s'), 133.0 (d'), 134.7 (s'), 166.3 (s'); exact mass *m/z* calcd for $C_{26}H_{32}NaO_8S$ 527.17156, found 527.1719.

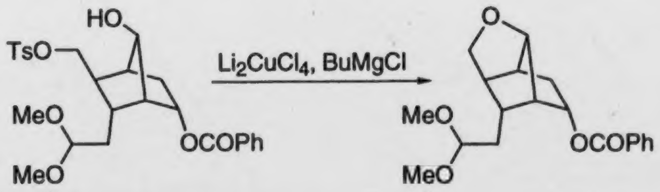
Benzoic Acid (2-*endo*, 9-*endo*)-6-(2,2-Dimethoxyethyl)-5-oxatricyclo[4.3.0^{1,6}.0^{3,7}]non-9-yl Ester (33.1).



32.2 **33.1**

NaI (11.3 mg, 0.763 mmol) was added to a stirred solution of **32.2** (52.1 mg, 0.103 mmol) in DME (2.5 mL), and the resulting suspension was refluxed for 11 h. The cooled mixture was diluted with Et_2O (25 mL) and washed with brine (2 x 20 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 16 cm), using 1:4 EtOAc-hexanes, gave **33.1** (18.8 mg, 55%) as a solid: mp 35-37 °C; FTIR (CH_2Cl_2 cast) 1716 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 1.40-1.44 (m, 1 H), 1.75 (s, 1 H), 1.82-1.84 (m, 1 H), 1.93-2.05 (m, 3 H), 2.20-2.23 (m, 1 H), 2.59 (s, 1 H), 3.07 (s, 3 H), 3.12 (s, 3 H), 3.47-3.59 (m, 2 H), 3.99 (s, 1 H), 4.36-4.44 (m, 1 H), 5.08-5.16 (m, 1 H), 7.02-7.15 (m, 3 H), 8.16-8.20 (m, 2 H); ^{13}C NMR (C_6D_6, 100 MHz) δ 27.6 (t′), 35.1 (t′), 36.6 (d′), 44.2 (d′), 45.8 (d′), 50.5 (d′), 52.17 (q′), 52.23 (q′), 73.3 (d′), 76.9 (t′), 82.4 (d′), 104.1 (d′), 128.5 (d′), 129.9 (d′), 131.0 (s′), 132.9 (d′), 166.0 (s′); exact mass *m/z* calcd for $C_{19}H_{24}NaO_5$ 355.15214, found 355.1522.

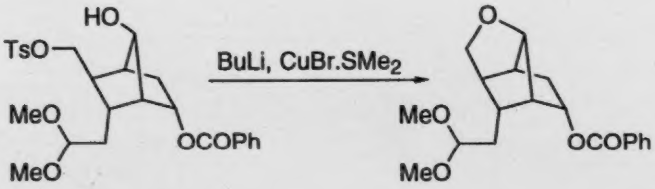
Benzoic Acid (2-*endo*, 9-*endo*)-6-(2,2-Dimethoxyethyl)-5-oxatricyclo$[4.3.0^{1,6}.0^{3,7}]$non-9-yl Ester (33.1).



32.2 **33.1**

Li_2CuCl_4[18] (0.1 M in THF, 0.70 mL, 0.070 mmol) was added to a stirred and cooled (0 °C) solution of BuMgCl (2 M in THF, 0.35 mL, 0.70 mmol) in THF (1 mL). The resulting solution was stirred at 0 °C for 10 min and **32.2** (70.6 mg, 0.140 mmol) was tipped in. The cold bath was left in place, but not recharged, and stirring was continued for 1 h, by which time the solution had attained room temperature. The mixture was quenched by addition of water (0.5 mL), and extracted with Et_2O (20 mL). The organic extract was washed with brine (2 x 20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 11 cm), using 1:4 EtOAc-hexanes, gave cyclized compound **33.1** (36.6 mg, 79%), spectroscopically identical to the material described in the previous experiment.

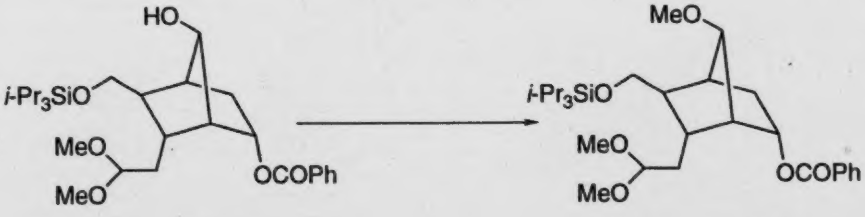
Benzoic Acid (2-*endo*, 9-*endo*)-6-(2,2-Dimethoxyethyl)-5-oxatricyclo[4.3.0^{1,6}.0^{3,7}]non-9-yl Ester (33.1).



32.2 **33.1**

$CuBr.SMe_2$ (137 mg, 0.666 mmol) was added to a stirred and cooled (-35 °C) solution of BuLi (2.5 M in hexanes, 0.50 mL, 1.3 mmol) in THF (2 mL). Stirring at -35 °C was continued for 50 min, and the solution was then cooled to -70 °C. Then **32.2** (103.2 mg, 0.245 mmol) was tipped into the solution, and the mixture was stirred for 4 h, during which time the temperature rose to -30 °C. The mixture was quenched with water (1 mL) and diluted with Et_2O (30 mL). The organic extract was washed with brine (2 x 20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 11 cm), using 1:4 to 1:3 EtOAc-hexanes, gave cyclized compound **33.1** (52.1 mg, 54%) as a solid.

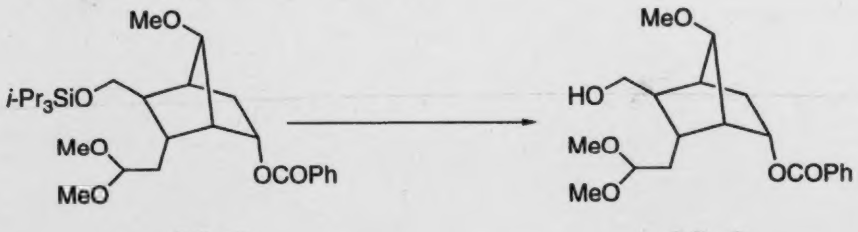
Benzoic Acid (2-*endo*, 5-*exo*, 6-*endo*, 7-*anti*)-6-(2,2-Dimethoxyethyl)-7-methoxy-5-[[(triisopropylsilanyl)oxy]methyl]bicyclo[2.2.1]hept-2-yl Ester (35.1).



34.1 **35.1**

Ag_2O (684.9 mg, 2.95 mmol) and MeI (1.0 mL, 16 mmol) were added to a stirred solution of **34.1** (499.2 mg, 0.987 mmol) in MeCN (2 mL) and the mixture was refluxed for 4 h (protection from light). At this stage, examination by TLC (silica, 1:3 EtOAc-hexane) showed complete conversion. Evaporation of the solvent and filtration of the residue through flash chromatography silica gel (3.5 x 2.5 cm), using 1:10 EtOAc-hexanes, gave **35.1** (412.1 mg, 80%) as an oil: FTIR (CH_2Cl_2 cast) 1719 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 1.05-1.22 (m, 22 H), 1.70-1.79 (m, 1 H), 2.04-2.18 (m, 1 H), 2.22-2.27 (m, 1 H), 2.31-2.47 (m, 3 H), 2.54-2.72 (m, 1 H), 2.97 (s, 3 H), 3.08-3.16 (m, 4 H), 3.17 (s, 3 H), 3.91 (d, J = 7.5 Hz, 2 H), 4.58-4.68 (m, 1 H), 5.68-5.79 (m, 1 H), 7.07-7.19 (m, 3 H), 8.19-8.28 (m, 2 H); ^{13}C NMR (C_6D_6, 100 MHz) δ 12.4 (d′), 18.3 (q′), 35.7 (t′), 36.7 (t′), 37.3 (d′), 41.2 (d′), 45.4 (d′), 51.3 (d′ or q′), 52.3 (d′ or q′), 53.4 (d′ or q′), 56.4 (q′), 67.5 (t′), 74.5 (d′), 86.9 (d′), 103.8 (d′), 128.5 (d′), 130.0 (d′), 131.1 (s′), 132.8 (d′), 166.3 (s′); exact mass *m/z* calcd for $C_{29}H_{48}NaO_6Si$ 543.31179, found 543.3120.

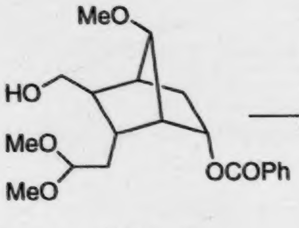
Benzoic Acid (2-*endo*, 5-*exo*, 6-*endo*, 7-*anti*)-6-(2,2-Dimethoxyethyl)-5-hydroxymethyl-7-methoxybicyclo-[2.2.1]hept-2-yl Ester (35.2).



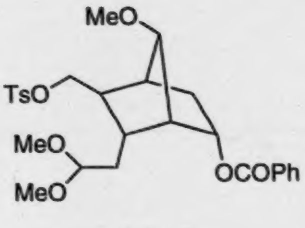
35.1 **35.2**

Bu$_4$NF (1 M in THF, 1.40 mL, 1.40 mmol) was added to a stirred solution of **35.1** (401 mg, 0.771 mmol) in THF (2.0 mL), and stirring was continued for 4 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (3.0 mL) and extracted with Et_2O (25 mL). The organic extract was washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 16 cm), using 1:1 to 2:1 EtOAc-hexanes, gave **35.2** (185 mg, 66%) as an oil: FTIR (CH_2Cl_2 cast) 1716, 3422 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 1.10 (dd, J = 13.5, 4.5 Hz, 1 H), 1.39-1.45 (m, 1 H), 1.95-2.08 (m, 2 H), 2.14-2.25 (m, 3 H), 2.40-2.46 (m, 1 H), 2.56-2.62 (m, 1 H), 2.85 (s, 3 H), 2.98-3.02 (m, 1 H), 3.09 (s, 3 H), 3.11 (s, 3 H), 3.67-3.71 (m, 2 H), 4.58 (t, J = 5.7 Hz, 1 H), 5.13-5.20 (m, 1 H), 7.05-7.18 (m, 3 H), 8.17-8.27 (m, 2 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 35.6 (t′), 36.8 (d′), 37.1 (t′), 42.7 (d′), 45.8 (d′), 51.3 (d′ or q′), 52.5 (d′ or q′), 53.1 (d′ or q′), 56.5 (q′), 65.7 (t′), 74.4 (d′), 86.4 (d′), 103.8 (d′), 128.6 (d′), 130.0 (d′), 131.0 (s′), 132.9 (d′), 166.2 (s′); exact mass *m/z* calcd for $C_{20}H_{28}NaO_6$ 387.17836, found 387.1785.

Benzoic Acid (2-*endo*, 5-*exo*, 6-*endo*, 7-*anti*)-6-(2,2-Dimethoxyethyl)-7-methoxy-5-(toluene-4-sufonyloxymethyl)bicyclo[2.2.1]hept-2-yl Ester (35.3).



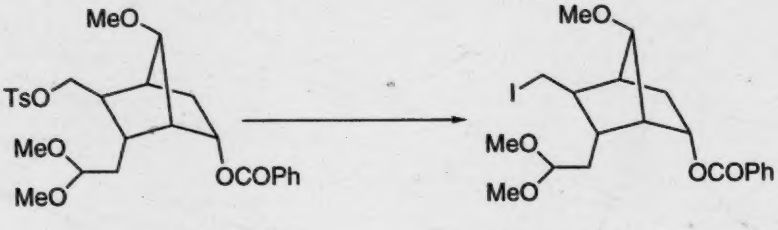
35.2



35.3

Pyridine (0.13 mL, 1.6 mmol), DMAP (1.2 mg, 0.001 mmol) and TsCl (164.6 mg, 0.864 mmol) were added to a stirred and cooled (0 °C) solution of **35.2** (178.1 mg, 0.489 mmol) in CH_2Cl_2 (2 mL), and stirring was continued overnight. The mixture was diluted with EtOAc (25 mL), washed with water (25 mL), saturated aqueous $CuSO_4$ (25 mL), and brine (25 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 9 cm), using 1:5 to 1:4 EtOAc-hexanes, gave **35.3** (240.5 mg, 95%) as an oil: FTIR (CH_2Cl_2 cast) 1716 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 1.68-1.73 (m, 1 H), 1.82 (s, 3 H), 1.89-1.95 (m, 1 H), 1.99-2.04 (m, 1 H), 2.06-2.13 (m, 1 H), 2.14-2.24 (m, 2 H), 2.50-2.54 (m, 1 H), 2.77 (s, 3 H), 2.94-2.98 (m, 1 H), 3.03 (s, 3 H), 3.06 (s, 3 H), 4.24-4.31 (m, 2 H), 4.31-4.41 (m, 1 H), 5.05-5.09 (m, 1 H), 6.71 (d, J = 8.5 Hz, 2 H), 7.10-7.16 (m, 3 H), 7.79 (d, J = 8.5 Hz, 2 H), 8.12-8.17 (m, 2 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 21.2 (q'), 35.4 (t'), 35.9 (t'), 36.9 (d'), 41.1 (d'), 45.9 (d'), 49.4 (d' or q'), 51.7 (d' or q'), 52.3 (d' or q'), 56.5 (q'), 73.8 (t'), 74.0 (d'), 86.5 (d'), 103.7 (d'), 128.6 (d'), 129.7 (d'), 129.9 (d'), 130.8 (s'), 133.0 (d'), 134.7 (s'), 143.9 (s'), 166.1 (s'); no mass spectrum was measured.

Benzoic Acid (2-*endo*, 5-*exo*, 6-*endo*, 7-*anti*)-6-(2,2-Dimethoxyethyl)-5-iodomethyl-7-methoxybicyclo-[2.2.1]hept-2-yl Ester (34.2).

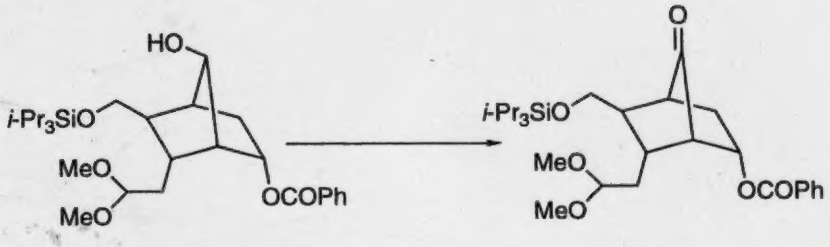


35.3 **34.2**

NaI (280.1 mg, 1.87 mmol) was added to a stirred solution of **35.3** (235.5 mg, 0.456 mmol) in DME (2.0 mL) and the suspension was refluxed for 22 h. Examination of the mixture by TLC (silica, 1:3 EtOAc-hexane) showed complete conversion. The mixture was cooled and partitioned between water (20 mL) and Et_2O (20 mL). The organic extract was washed with saturated aqueous $Na_2S_2O_3$ (20 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 12 cm), using 1:10 to 1:4 EtOAc-hexanes, gave **34.2** (146 mg, 68%) as an oil: FTIR (CH_2Cl_2 cast) 1716 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.91-0.96 (m, 1 H), 1.68-1.79 (m, 1 H), 1.91-2.32 (m, 5 H), 2.64-2.69 (m, 1 H), 2.83 (s, 3 H), 2.96-2.99 (m, 1 H), 3.04 (s, 3 H), 3.11 (s, 3 H), 3.26-3.40 (m, 2 H), 4.40-4.44 (m, 1 H), 5.01-5.07 (m, 1 H), 7.08-7.15 (m, 3 H), 8.14-8.18 (m, 2 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 12.3 (t'), 34.9 (t'), 36.0 (t'), 41.5 (d'), 44.4 (d'), 46.9 (d'), 51.2

(d′ or q′), 52.3 (d′ or q′), 53.5 (d′ or q′), 56.6 (q′), 73.7 (d′), 86.2 (d′), 103.5 (d′), 128.6 (d′), 130.0 (d′), 130.7 (s′), 132.9 (d′), 166.1 (s′); exact mass *m/z* calcd for $C_{20}H_{27}NaO_5I$ 497.08010, found 497.0804.

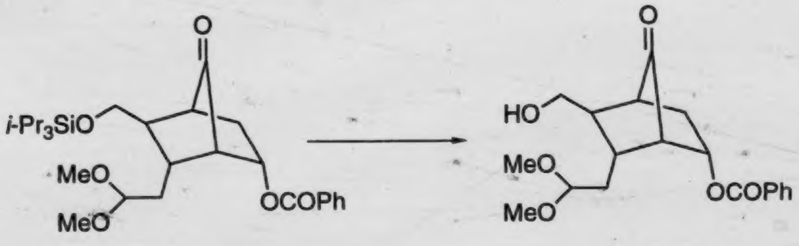
Benzoic Acid (2-*endo*, 5-*exo*, 6-*endo*)-6-(2,2-Dimethoxyethyl)-7-oxo-5-[[(triisopropylsilanyl)oxy]-methyl]bicyclo[2.2.1]hept-2-yl Ester (40.1).



34.1 **40.1**

Dess-Martin periodinane (994 mg, 2.34 mmol) was added to a stirred solution of **34.1** (668 mg, 1.32 mmol) and pyridine (1.0 mL, 12 mmol) in CH_2Cl_2 (10 mL). Stirring was continued overnight, and the mixture was then filtered through a pad of Celite (5 x 1 cm). The pad was washed with EtOAc (100 mL) and the filtrate was washed with saturated aqueous $NaHCO_3$ (20 mL), saturated aqueous $Na_2S_2O_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 10 cm), using 1:10 EtOAc-hexanes, gave **40.1** (631 mg, 95%) as an oil: FTIR (CH_2Cl_2 cast) 1721, 1780 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.99-1.11 (m, 21 H), 1.31-1.35 (m, 1 H), 1.61-1.65 (m, 1 H), 2.06-2.22 (m, 3 H), 2.24-2.30 (m, 2 H), 2.53-2.55 (m, 1 H), 3.02 (s, 3 H), 3.05 (s, 3 H), 3.42-3.46 (m, 1 H), 3.54-3.57 (m, 1 H), 4.37-4.39 (m, 1 H), 5.39-5.41 (m, 1 H), 7.08-7.15 (m, 3 H), 8.13-8.15 (m, 2 H); ^{13}C NMR (C_6D_6, 100 MHz) δ 12.2 (d′), 18.2 (q′), 33.5 (d′), 34.8 (t′), 37.2 (t′), 45.2 (d′), 48.7 (d′), 49.1 (d′), 51.9 (q′), 52.3 (q′), 65.8 (t′), 70.9 (d′), 103.1 (d′), 128.6 (d′), 130.0 (d′), 130.6 (s′), 133.0 (d′), 165.9 (s′), 207.4 (s′); exact mass *m/z* calcd for $C_{28}H_{44}NaO_6Si$ 527.28049, found 527.2812.

Benzoic Acid (2-*endo*, 5-*exo*, 6-*endo*)-6-(2,2-Dimethoxyethyl)-5-hydroxymethyl-7-oxobicyclo[2.2.1]-hept-2-yl Ester (39.1).

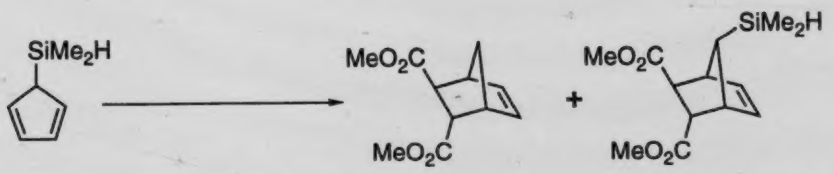


40.1 **39.1**

Bu$_4$NF (1 M in THF, 4.0 mL, 4.0 mmol) was added to a stirred solution of **40.1** (991 mg, 1.97 mmol) in THF (15 mL). Stirring was continued for 4 h, and the mixture was partition between CH_2Cl_2 (50 mL) and brine (50 mL). The aqueous layer was extracted with CH_2Cl_2 (50 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 18 cm),

using 1:2 EtOAc-hexanes, gave **39.1** (432 mg, 63%) as a solid: mp 55-57 °C; FTIR (CH_2Cl_2 cast) 1717, 1777, 3411 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 1.25-1.30 (m, 1 H), 1.45-1.52 (m, 1 H), 1.86-1.94 (m, 2 H), 1.98-2.07 (m, 1 H), 2.09-2.27 (m, 2 H), 2.46-2.51 (m, 1 H), 2.97 (s, 3 H), 3.00 (s, 3 H), 3.02-3.24 (m, 3 H), 4.32-4.38 (m, 1 H), 5.33-5.41 (m, 1 H), 7.03-7.17 (m, 3 H), 8.07-8.16 (m, 2 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 33.8 (d′), 34.7 (t′), 37.1 (t′), 45.0 (d′), 48.4 (d′), 48.7 (d′), 51.7 (q′), 52.3 (q′), 64.9 (t′), 70.8 (d′), 102.9 (d′), 128.6 (d′), 129.9 (d′), 130.6 (s′), 133.1 (d′), 165.9 (s′), 208.0 (s′); exact mass *m/z* calcd for $C_{19}H_{24}NaO_6$ 371.14706, found 371.1473.

(2-*endo*, 3-*exo*, 7-*anti*)-7-(Dimethylsilanyl)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic Acid Dimethyl Ester (44.1) and (2-*endo*, 3-*exo*)-Bicyclo-[2.2.1]hept-5-ene-2,3-dicarboxylic Acid Dimethyl Ester (45.1).

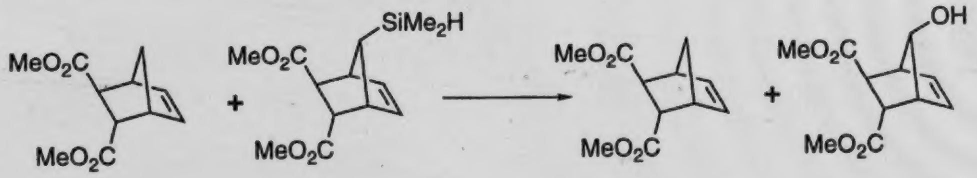


43.2 **45.1** **44.1**

Me$_2$AlCl (1 M in hexanes, 9.80 mL, 9.80 mmol) was added dropwise by syringe over 5 min to a stirred and cooled (-76 °C) solution of dimethyl fumarate (1.452 mg, 9.78 mmol).

Stirring was continued for 10 min, and a solution of 5-dimethylsilylcyclopentadiene[19] (ca 26.52 g, ca 27.4 mmol) in hexanes (37 mL) was added dropwise by cannula. Stirring was continued for 5 h at -76 °C and the mixture was quenched by addition of 10% aqueous $NaHCO_3$ (100 mL). The mixture was extracted with Et_2O (100 mL), and the organic extract was washed with brine (2 x 100 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3.5 x 20 cm), using 1:10 EtOAc-hexanes, gave a mixture of **45.1** and **44.1** (2.11 g, yield of **44.1** by calculation is ca 53%). The material was used directly without characterization.

(2-*endo*, 3-*exo*, 7-*anti*)-7-Hydroxybicyclo[2.2.1]-hept-5-ene-2,3-dicarboxylic Acid Dimethyl Ester (42.3 and (2-*endo*, 3-*exo*)-Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic Acid Dimethyl Ester (45.1).



45.1 **44.1** **45.1** **42.3**

Bu_4NF (1 M in THF, 3.60 mL, 3.60 mmol), $KHCO_3$ (128.3 mg, 1.28 mmol) and H_2O_2 (30 w/w%, 1.0 mL, 9.7 mmol) were added in that order to a stirred solution of a mixture of **45.1** (ca 80.3 mg, ca 0.382 mmol) and **44.1** (ca 162.8 mg, 0.598 mmol) in

MeOH (1.5 mL) and THF (1.5 mL). Stirring was continued at room temperature overnight. The mixture was diluted with brine (10 mL) and extracted with Et_2O (3 x 25 mL). The organic extracts were combined and the aqueous phase (**X**) was saved for acidification at a later stage. The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ (25 mL), 10% aqueous $NaHCO_3$ (25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 20 cm), using 1:10 EtOAc-hexanes, gave **45.1** (80.3 mg) and **42.3** (47.1 mg) as oils.

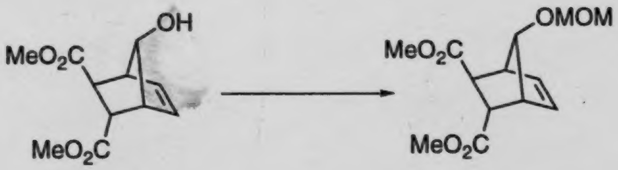
The aqueous phase (**X**) was acidified to pH 2 with 2 N hydrochloric acid, and extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine (2 x 30 mL) and dried ($MgSO_4$). Evaporation of the solvent gave a crude mixture as an oil (160 mg). This material (160 mg) was dissolved in acetone (3.0 mL), and K_2CO_3 (447.4 mg, 3.24 mmol) and Me_2SO_4 (0.30 mL, 3.2 mmol) were added to the solution. The mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc (25 mL), washed with brine (2 x 20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using 1:3 to 3:1 EtOAc-hexanes, gave **42.3** (11.0 mg), bringing the total yield of **42.3** to 43%. The above procedure was used because some ester hydrolysis occurred in the oxidation step.

Compound **45.1** had: FTIR (CH_2Cl_2 cast) 1731 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 1.27 (d, J = 8.5 Hz, 1 H), 1.58 (d, J = 8.5 Hz, 1 H), 2.84-2.89 (m, 1 H), 2.96-2.99 (m, 1 H), 3.09-3.13

(m, 1 H), 3.26 (s, 3 H), 3.33 (s, 3 H), 3.46-3.51 (m, 1 H), 5.96-6.02 (m, 2 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 46.0 (d′), 47.5 (t′), 47.6 (d′), 48.1 (d′), 48.4 (d′), 51.4 (q′), 51.7 (q′), 135.4 (d′), 137.6 (d′), 173.0 (s′), 174.4 (s′); exact mass *m/z* calcd for $C_{11}H_{14}NaO_4$ 233.07898, found 233.0788

Compound **42.3** had: FTIR (CH_2Cl_2 cast) 1731, 3436 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 2.58-2.77 (broad peak, -OH), 2.75 (d, *J* = 5.2 Hz, 1 H), 2.89-2.96 (m, 1 H), 2.97-3.04 (m, 1 H), 3.21 (s, 3 H), 3.27 (s, 3 H), 4.12-4.17 (m, 1 H), 5.73-5.83 (m, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 44.6 (d′), 45.4 (d′), 50.5 (d′), 52.1 (d′ or q′), 52.2 (d′ or q′), 52.3 (d′ or q′), 84.9 (d′), 131.9 (d′), 133.9 (d′), 172.6 (s′), 173.6 (s′); exact mass *m/z* calcd for $C_{11}H_{14}NaO_5$ 249.07389, found 249.0735.

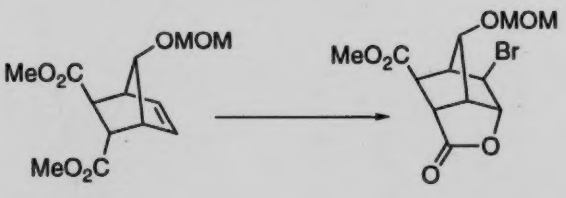
(2-*endo*, 3-*exo*, 7-*anti*)-7-(Methoxymethoxy)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic Acid Dimethyl Ester (46.1).



42.3 **46.1**

MOMCl (1.73 mL, 22.8 mmol) was added to a stirred and cooled (0 °C) solution of **42.3** (1.508 g, 6.53 mmol) and *i*-Pr_2NEt (4.60 mL, 26.5 mmol) in CH_2Cl_2 (22 mL). The cold bath was left in place, but not recharged, and stirring was continued overnight. At this point, examination by TLC (silica, 1:3 EtOAc-hexane) suggested that ca 50% conversion had occurred. *i*-Pr_2NEt (4.80 mL, 22.6 mmol), DMAP (15.9 mg, 0.13 mmol) and MOMCl (1.50 mL, 19.7 mmol) were added to the solution at 0 °C. The cold bath was left in place, but not recharged, and stirring was continued overnight. The reaction was quenched with 5% hydrochloric acid (25 mL). The organic phase was separated, washed with brine (2 x 40 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 1:3 to 3:1 EtOAc-hexanes, gave **42.3** (272 mg) and **46.1** (731 mg, 49% based on conversion). Compound **46.1** had: FTIR (CH_2Cl_2 cast) 1733 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 2.86 (d, J = 5.1 Hz, 1 H), 3.04 (s, 3 H), 3.18-3.25 (m, 4 H), 3.27 (s, 3 H), 3.33-3.37 (m, 1 H), 3.39-3.44 (m, 1 H), 4.03-4.07 (m, 1 H), 4.33 (s, 2 H), 5.94-6.01 (m, 2 H); exact mass m/z calcd for $C_{13}H_{18}NaO_6$ 293.10011, found 293.1005. A ^{13}C NMR spectrum was not run.

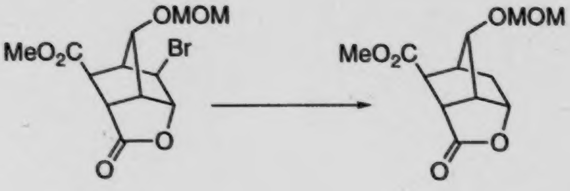
(2-*exo*, 9-*exo*, 8-*anti*)-2-Bromo-8-(methoxymethoxy)-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-carboxylic Acid Methyl Ester (46.2).



46.1 **46.2**

Br_2 (0.15 mL, 2.9 mmol) was added to a stirred and cooled (0 °C) solution of **46.1** (706 mg, 2.61 mmol) in CH_2Cl_2 (20 mL). The cold bath was left in place, but not recharged, and stirring was continued overnight. The mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ (15 mL), and the organic phase was washed with brine (2 x 30 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 13 cm), using 1:10 to 1:3 EtOAc-hexanes, gave **46.2** (578 mg, 66%): FTIR (CH_2Cl_2 cast) 1734, 1796 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 2.07-2.09 (m, 1 H), 2.40-2.43 (m, 1 H), 2.70-2.77 (m, 2 H), 3.04 (s, 3 H), 3.16 (s, 3 H), 3.31 (s, 1 H), 4.06-4.09 (m, 1 H), 4.26 (d, J = 9.4 Hz, 1 H), 4.33 (d, J = 9.4 Hz, 1 H), 4.88-4.93 (m 1 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 39.2 (d'), 47.7 (d'), 48.8 (d'), 49.0 (d'), 49.1 (d'), 52.3 (q'), 55.8 (q'), 82.2 (d'), 88.6 (d'), 95.9 (t'), 170.1 (s'), 175.4 (s'); exact mass *m/z* calcd for $C_{12}H_{15}{}^{79}BrNaO_6$ 356.99497, found 356.9944.

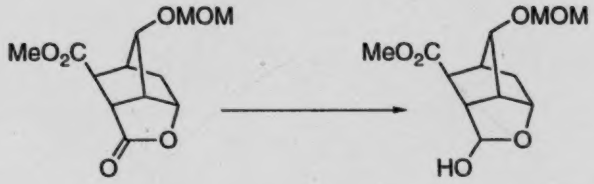
(9-*exo*, 8-*anti*)-8-(Methoxymethoxy)-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-carboxylic Acid Methyl Ester (46.3).



46.2 **46.3**

A solution of **46.2** (578 mg, 1.73 mmol), AIBN (42.9 mg, 0.262 mmol) and Bu_3SnH (0.52 mL, 1.9 mmol) in PhH (10 mL) was refluxed for 3.5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3.5 x 15 cm), using 1:10 to 1:2 EtOAc-hexanes, gave **46.3** (365 mg, 83%): FTIR (CH_2Cl_2 cast) 1733, 1783 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 1.08 (d, J = 14 Hz, 1 H), 1.93-1.98 (m, 1 H), 2.35-2.39 (m, 2 H), 2.43-2.47 (m, 1 H), 2.85-2.87 (m, 1 H), 2.91 (s, 3 H), 3.17 (s, 3 H), 3.98 (s, 1 H), 4.14 (s, 2 H), 4.49-4.52 (m, 1 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 34.7 (t′), 40.7 (d′), 43.2 (d′), 47.6 (d′), 48.2 (d′), 52.0 (q′), 55.4 (q′), 79.9 (d′), 83.3 (d′), 96.2 (t′), 171.9 (s′), 177.0 (s′); exact mass *m/z* calcd for $C_{12}H_{16}NaO_6$ 279.08446, found 279.0849.

(9-*exo*, 8-*anti*)-5-Hydroxy-8-(methoxymethoxy)-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-carboxylic Acid Methyl Ester (46.4).

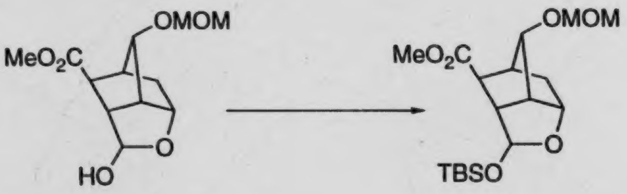


46.3 **46.4**

DIBAL (1 M in THF, 1.40 mL, 1.40 mmol) was added to a stirred and cooled (-76 °C) solution of **46.3** (145 mg, 0.566 mmol) in THF (5.0 mL). Stirring at -76 °C was continued for 4 h, and the mixture was quenched by addition of MeOH (3 mL). The mixture was taken up in EtOAc (75 mL), washed with 5% hydrochloric acid (5 mL), 10% aqueous $NaHCO_3$ (10 mL) and brine (2 x 10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 10 cm), using 1:2 to 1:1 EtOAc-hexanes, gave **46.4** (82 mg, 56%) as an oily mixture of two isomers: FTIR (CH_2Cl_2 cast) 1732, 3412 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 1.18 (d, J = 12.5 Hz, 1 H), 2.01-2.06 (m, 1 H), 2.11-2.16 (m, 1 H), 2.37-2.42 (m, 1 H), 2.40-2.48 (m, 1 H), 2.69-2.75 (m, 1 H), 2.97-3.02 (m, 4 H), 3.26 (s, 3 H), 4.27-4.33 (m, 3 H), 4.70-4.72 (m, 1 H), 4.99-5.04 (m, 1 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 37.1 (t′), 42.0 (d′), 47.2 (d′), 47.35 (d′), 47.39 (d′), 51.6 (q′), 55.3 (q′), 80.1 (d′), 84.0 (d′), 96.3 (t′), 102.5 (d′), 173.5 (s′); exact mass m/z calcd for $C_{12}H_{18}NaO_6$ 281.10011, found 281.1004.

(9-*exo*, 8-*anti*)-5-(*tert*-Butyldimethylsilanyloxy]-8-(methoxymethoxy)-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-

carboxylic Acid Methyl Ester (46.5).

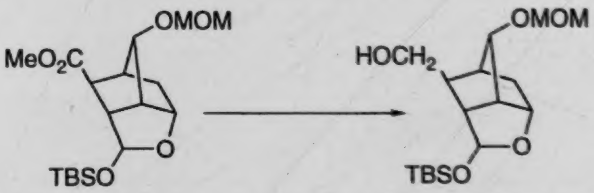


46.4 **46.5**

Et_3N (0.36 mL, 2.6 mmol), DMAP (one grain) and *t*-$BuMe_2SiCl$ (250 mg, 1.66 mmol) were added to a stirred solution of **46.4** (200.1 mg, 0.776 mmol) in CH_2Cl_2 (5.5 mL). Stirring was continued for 13 h, and then additional portions of Et_3N (0.40 mL, 2.9 mmol), DMAP (26.1 mg, 0.214 mmol) and *t*-$BuMe_2SiCl$ (240.1 mg, 1.59 mmol) were added. Stirring was continued for another 20 h. The mixture was diluted with EtOAc (20 mL), washed with brine (2 x 20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 10 cm), using 1:20 to 7:10 EtOAc-hexanes, gave **46.5** (253.2 mg, 88%) as a single isomer (of unestablished stereochemistry), which was an oil: FTIR ($CHCl_3$ cast) 1737 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.15 (s, 3 H), 0.17 (s, 3 H), 0.97 (s, 9 H), 1.20 (d, J = 12.5 Hz, 1 H), 2.08-2.09 (m, 1 H), 2.11-2.16 (m, 1 H), 2.49-2.53 (m, 1 H), 2.72-2.77 (m, 1 H), 3.02-3.08 (m, 4 H), 3.25 (s, 3 H), 4.30-4.38 (m, 3 H), 4.66-4.72 (m, 1 H), 5.22 (s, 1 H); ^{13}C NMR (C_6D_6, 125 MHz) δ -4.6 (q'), -4.0 (q'), 18.2 (s'), 26.1 (q'), 37.1 (t'), 42.0 (d'), 47.0 (d'), 47.3 (d'), 48.7 (d'), 51.5

(q′), 55.2 (q′), 80.0 (d′), 83.9 (d′), 96.2 (t′), 103.0 (d′), 173.7 (s′); exact mass *m/z* calcd for $C_{18}H_{32}NaO_6Si$ 395.18659, found 395.1869.

(9-*exo*, 8-*anti*)-[5-(*tert*-Butyldimethylsilanyloxy)-8-(methoxymethoxy)-4-oxatricyclo[4.2.1.0^{3,7}]non-9-yl]methanol (46.6).

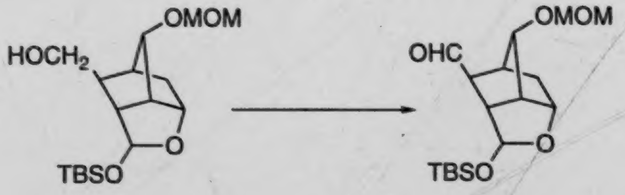


46.5 **46.6**

DIBAL (1 M in THF, 2.0 mL, 2.0 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **46.5** (251.1 mg, 0.674 mmol) in CH_2Cl_2 (8.0 mL). Stirring at -76 °C was continued for 7 h and then overnight at room temperature. The mixture was quenched by addition of MeOH (2.0 mL) and was then diluted with EtOAc (25 mL). Saturated aqueous potassium sodium tartrate (25 mL) was added and the mixture was stirred for 1 h. The organic layer was separated and washed with brine (25 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 9.5 cm), using 1:10 to 1:1 EtOAc-hexanes, gave **46.6** (203.2 mg, 87%) as a solid: mp 85-87 °C; FTIR ($CHCl_3$ cast) 3445 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.19 (s, 6 H), 1.00 (s, 9 H), 1.34 (d, *J* =

12.5 Hz, 1 H), 1.38-1.42 (m, 1 H), 1.64-1.69 (m, 1 H), 1.87-1.93 (m, 1 H), 2.09 (s, 1 H), 2.13-2.22 (m, 1 H), 2.98-3.02 (m, 1 H), 3.07-3.17 (m, 5 H), 4.06 (s, 1 H), 4.37 (s, 2 H), 4.72-4.77 (m, 1 H), 5.24 (s, 1 H); ^{13}C NMR (C_6D_6, 125 MHz) δ -4.6 (q′), -3.9 (q′), 18.2 (s′), 26.1 (q′), 37.9 (t′), 40.2 (d′), 46.0 (d′), 47.5 (d′), 48.2 (d′), 55.1 (q′), 64.5 (t′), 80.3 (d′), 83.5 (d′), 96.0 (t′), 103.4 (d′); exact mass *m/z* calcd for $C_{17}H_{32}NaO_5Si$ 367.19167, found 367.1914.

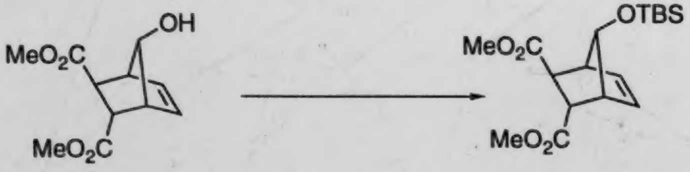
(9-*exo*, 8-*anti*)-5-(*tert*-Butyldimethylsilanyloxy)-8-(methoxymethoxy)-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-carbaldehyde (46.7).



46.6 **46.7**

Dess-Martin periodinane (217.9 mg, 0.514 mmol) was added to a stirred solution of **46.6** (80.0 mg, 0.232 mmol) and pyridine (0.40 mL, 4.9 mmol) in CH_2Cl_2 (10 mL). Stirring was continued overnight, CH_2Cl_2 (10 mL) was added, and the mixture was washed with saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were washed with brine (2 x 20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 13 cm), using 1:10 EtOAc-hexanes, gave **46.7** (60.1 mg, 76%) as an oil: FTIR ($CHCl_3$ cast) 1726 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.17 (s, 6 H), 0.99 (s, 9 H), 1.13 (d, *J* = 12.5 Hz, 1 H), 1.56-1.59 (m, 1 H), 2.07-2.12 (m, 1 H), 2.23 (s, 1 H), 2.63-2.65 (m, 1 H), 2.94-2.96 (m, 1 H), 3.00 (s, 3 H), 3.75 (s, 1 H), 4.25 (s, 2 H), 4.64-4.67 (m, 1 H), 5.05 (s, 1 H), 9.07 (s, 1 H); ^{13}C NMR (C_6D_6, 125 MHz) δ -4.7 (q′), -3.9 (q′), 18.2 (s′), 26.1 (q′), 37.0 (q′), 39.1 (d′), 44.7 (d′), 47.4 (d′), 54.6 (d′ or q′), 55.2 (d′ or q′), 80.1 (d′), 83.1 (d′), 96.1 (t′), 102.9 (d′), 199.2 (d′); exact mass *m/z* calcd for $C_{17}H_{30}NaO_5Si$ 365.17602 found 365.1765.

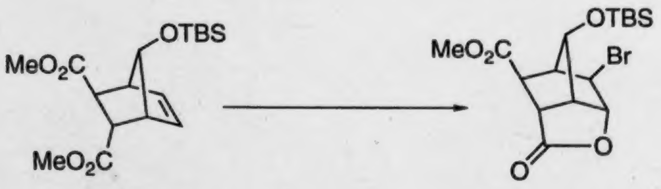
(2-*endo*, 3-*exo*, 7-*anti*)-7-(*tert*-Butyldimethylsilanyloxy)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic Acid Dimethyl Ester (47.1).



42.3 **47.1**

Imidazole (85.9 mg, 1.26 mmol), DMAP (20.3 mg, 0.166 mmol) and *t*-$BuMe_2SiCl$ (157.3 mg, 1.04 mmol) were added to a stirred solution of **42.3** (115 mg, 0.509 mmol) in DMF (3.0 mL), and stirring was continued overnight. The mixture was poured into water (15 mL) and extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with brine (2 x 20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 9 cm), using 1:10 EtOAc-hexanes, gave **47.1** (139 mg, 80%) as an oil: FTIR ($CHCl_3$ cast) 1735 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.00 (s, 6 H), 0.89 (s, 9 H), 2.86 (d, J = 5.1 Hz, 1 H), 3.01-3.06 (m, 1 H), 3.15-3.18 (m, 1 H), 3.24 (s, 3 H), 3.30 (s, 3 H), 3.38-3.41 (m, 1 H), 4.32-4.35 (m, 1 H), 5.93-5.97 (m, 2 H); ^{13}C NMR (C_6D_6, 100 MHz) δ -4.79 (q′), -4.77 (q′), 18.3 (s′), 25.9 (q′), 45.1 (d′), 45.4 (d′), 51.0 (d′ or q′), 51.4 (d′ or q′), 51.6 (d′ or q′), 52.7 (d′ or q′), 86.1 (d′), 131.0 (d′), 133.4 (d′), 172.4 (s′), 174.2 (s′); exact mass m/z calcd for $C_{17}H_{28}NaO_5Si$ 363.16037 found 363.1607.

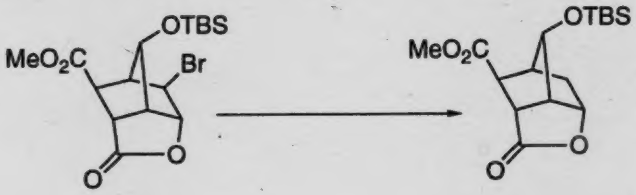
(2-*exo*, 9-*exo*, 8-*anti*)-2-Bromo-8-(*tert*-butyldimethylsilanyloxy)-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]-nonane-9-carboxylic Acid Methyl Ester (47.2).



47.1 **47.2**

Br_2 (0.78 mL, 15 mmol) was added dropwise by syringe to a stirred solution of **47.1** (4.1103 g, 12.07 mmol) in CH_2Cl_2 (60 mL). Stirring was continued overnight and the mixture was quenched by addition of saturated aqueous $NaHCO_3$. The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 20 cm), using 1:10 EtOAc-hexanes, gave **47.2** as solid (3.9112 g, 80%): mp 110-111 °C; FTIR ($CHCl_3$ cast) 1738, 1800 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ -0.03 (s, 3 H), 0.01 (s, 3 H), 0.90 (s, 9 H), 2.06 (s, 1 H), 2.23-2.26 (m, 1 H), 2.54 (s, 1 H), 2.63-2.66 (m, 1 H), 3.19 (s, 3 H), 3.35 (s, 1 H), 4.28 (s, 1 H), 4.89-4.91 (m, 1 H); ^{13}C NMR (C_6D_6, 125 MHz) δ -5.1 (q'), -4.9 (q'), 18.3 (s'), 26.0 (q'), 39.3 (d'), 47.4 (d'), 48.9 (d'), 50.8 (d' or q'), 51.0 (d' or q'), 52.1 (d' or q'), 79.1 (d'), 89.0 (d'), 170.6 (s'), 175.7 (s'); exact mass *m/z* calcd for $C_{16}H_{25}{}^{79}BrNaO_5Si$ 427.05523 found 427.0553.

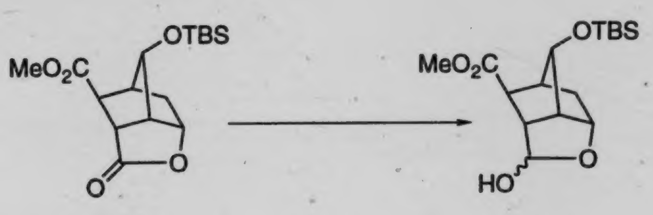
(9-*exo*, 8-*anti*)-8-(*tert*-butyldimethylsilanyloxy)-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-carboxylic Acid Methyl Ester (47.3).



47.2 **47.3**

A solution of Bu_3SnH (3.10 mL, 11.5 mmol) and AIBN (234.1 mg, 1.43 mmol) were added to a solution of **47.2** (3.8912 g, 9.59 mmol) in PhH (80 mL) was refluxed for 4 h, and the solvent was then concentrated to ca 30 mL. Flash chromatography of the residue (the solution was applied directly to the column) over silica gel (3.5 x 20 cm), using 1:5 EtOAc-hexanes, gave **47.3** as a solid (2.967 g, 95%): mp 79-80 °C; FTIR ($CHCl_3$ cast) 1736, 1785 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ -0.11 (s, 6 H), 0.82 (s, 9 H), 1.05-1.10 (m, 1 H), 1.99-2.06 (m, 1 H), 2.14-2.22 (m, 1 H), 2.18-2.27 (m, 1 H), 2.37 (s, 1 H), 2.80 (d, *J* = 5.2 Hz, 1 H), 3.20 (s, 3 H), 4.22 (br s, 1 H), 4.51 (t, *J* = 6.2 Hz, 1 H); ^{13}C NMR (C_6D_6, 125 MHz) δ -5.10 (q′), -5.07 (q′), 18.1 (s′), 25.8 (q′), 34.3 (t′), 40.8 (d′), 44.8 (d′), 46.9 (d′), 50.0 (d′), 51.8 (q′), 78.6 (d′), 80.3 (d′), 172.3 (s′), 177.3 (s′); exact mass *m/z* calcd for $C_{16}H_{26}NaO_5Si$ 349.14472 found 349.1447.

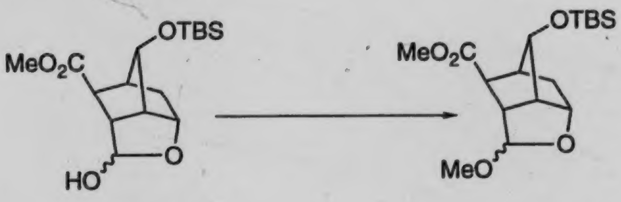
(9-*exo*, 8-*anti*)-8-(*tert*-Butyldimethylsilanyloxy)-5-hydroxy-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-carboxylic Acid Methyl Ester (47.4).



47.3 **47.4**

DIBAL (1 M in CH_2Cl_2, 0.68 mL, 0.68 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **47.3** (74.8 mg, 0.229 mmol) in THF (3.0 mL). Stirring at -76 °C was continued for 0.5 h, and the mixture was quenched by fast addition of MeOH (0.5 mL), and diluted with EtOAc (10 mL). Saturated aqueous potassium sodium tartrate (6.0 mL) was added and the mixture was stirred for 1 h. The organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.4 x 11.5 cm), using 1:5 to 1:3 EtOAc-hexanes, gave **47.4** as a solid (57.1 mg, 76%): mp 60-65 °C; FTIR ($CHCl_3$ cast) 1736, 3400 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) (major isomer) δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.17 (d, J = 13.0 Hz, 1 H), 2.04-2.09 (m, 1 H), 2.18-2.26 (m, 1 H), 2.27-2.32 (m, 1 H), 2.72-2.76 (m, 1 H), 2.87-2.93 (m, 1 H), 3.29 (s, 3 H), 3.33-3.38 (m, 1 H), 4.48-4.56 (m, 1 H), 4.70-4.78 (m, 1 H), 5.12-5.18 (m, 1 H); ^{13}C NMR (C_6D_6, 125 MHz) δ -4.92 (q′), -4.88 (q′), 18.2 (s′), 25.9 (q′), 36.6 (t′), 43.7 (d′), 47.2 (d′), 47.3 (d′), 49.1 (d′), 51.5 (q′), 79.2 (d′), 80.5 (d′), 102.8 (d′), 174.0 (s′); exact mass m/z calcd for $C_{16}H_{28}NaO_5Si$ 351.16037 found 351.1604.

(9-*exo*, 8-*anti*)-8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-carboxylic Acid Methyl Ester (47.5).

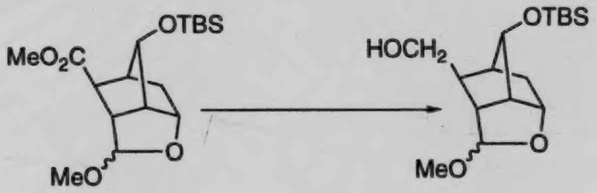


47.4 **47.5**

Lactols **47.4** (1.929 g, 5.87 mmol) and pyridinium *p*-toluenesulfonate (23.0 mg, 0.0915 mmol) were dissolved in $HC(OMe)_3$ (10 mL). The solution was stirred overnight, diluted with EtOAc (60 mL), washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (60 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 18.5 cm), using 1:5 to 1:3 EtOAc-hexanes, gave **47.5** (1.551 g, 77%) as two oily fractions, one being largely the major isomer and the other being largely the minor isomer: FTIR on mixture of isomers ($CHCl_3$ cast) 1736 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) (major isomer signals only) δ -0.02 (s, 3 H), -0.01 (s, 3 H), 0.86 (s, 9 H), 1.24 (d, *J* = 12.8 Hz, 1 H), 2.08-2.13 (m, 1 H), 2.22-2.30 (m, 1 H), 2.31-2.36 (m, 1 H), 2.77-2.82 (m, 1 H), 2.86-2.89 (m, 1 H), 3.19 (s, 3 H), 3.28 (s, 3 H), 4.52-4.56 (m, 1 H), 4.59 (s, 1 H), 4.68-4.74 (m, 1 H); ^1H NMR (C_6D_6, 400 MHz) (minor isomer signals) δ -0.01 (s, 6 H), 0.86 (s, 9 H), 1.43 (d, *J* = 13.6 Hz, 1 H), 2.22-2.28 (m, 1 H), 2.38-2.39 (m, 1 H), 2.41-2.44 (m, 1 H), 2.83-2.86 (m, 1 H), 3.27 (s, 3 H), 3.30 (s, 3 H), 3.33-3.34 (m, 1 H), 4.42 (s, 1 H), 4.59-4.62 (m, 1 H), 4.86-4.87 (m, 1 H); ^{13}C NMR (C_6D_6, 100 MHz) (major isomer signals) δ -4.98 (q′), -4.95 (q′), 18.1 (s′), 25.9 (q′), 36.8 (t′), 43.7 (d′), 46.4 (d′), 47.2 (d′), 49.5 (d′), 51.4 (q′), 54.3 (q′), 79.1 (d′), 80.4 (d′), 108.9 (d′), 173.9 (s′); ^{13}C NMR (C_6D_6, 100 MHz) (minor isomer signals) δ -4.96 (q′), -4.94 (q′), 18.1 (s′), 25.9 (q′), 35.9 (t′), 42.8 (d′), 43.1 (d′), 43.4 (d′), 51.3 (d′ or q′), 51.8 (d′ or q′), 56.3 (q′), 78.8 (d′), 80.1

(d′), 106.5 (d′), 174.8 (s′); exact mass (mixture of the isomers) *m/z* calcd for $C_{17}H_{30}NaO_5Si$ 365.17602 found 365.1759.

(9-*exo*, 8-*anti*)-[8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.$0^{3,7}$]non-9-yl]-methanol (47.6).



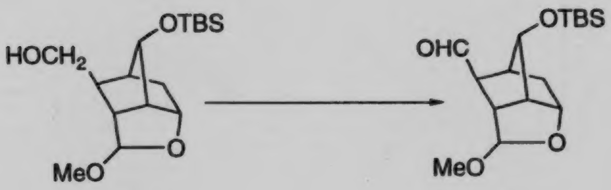
47.5 **47.6**

DIBAL (1 M in CH_2Cl_2, 8.50 mL, 8.50 mmol) was added dropwise over 10 min to a stirred and cooled (-76 °C) solution of **47.5** (mixture of isomers) (779 mg, 2.29 mmol) in THF (20 mL). The cold bath was left in place, but was not recharged, and stirring was continued overnight. The mixture was recooled to -76 °C and quenched by dropwise addition of MeOH (5.5 mL). EtOAc (60 mL) and saturated aqueous potassium sodium tartrate (50 mL) were added, and the mixture was stirred for 0.5 h at room temperature. The organic layer was separated, washed with brine (50 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 18.5 cm), using 1:10 to 1:2 EtOAc-hexanes, gave **47.6** as two isomers: A (101.5 mg, 14%) and B (568.1 mg, 79%). Isomer A had: mp 67-69 °C; FTIR (CH_2Cl_2 cast) 3435 cm^{-}

^{1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 0.00 (s, 6 H), 0.89 (s, 9 H), 1.26-1.33 (-OH, 1 H), 1.44 (d, J = 12.4 Hz, 1 H), 1.83-1.87 (m, 1 H), 1.94-1.98 (m, 1 H), 2.27-2.36 (m, 1 H), 2.38-2.47 (m, 2 H), 3.23-3.38 (m, 5 H), 4.27 (s, 1 H), 4.62-4.69 (m, 1 H), 4.86 (d, J = 4.0 Hz, 1 H); ^{13}C NMR (C_6D_6, 100 MHz) δ -4.6 (q′), 18.3 (s′), 26.1 (q′), 37.4 (t′), 41.68 (d′), 41.77 (d′), 43.3 (d′), 52.0 (d′), 56.5 (q′), 65.1 (t′), 78.5 (d′), 80.3 (d′), 107.3 (d′); exact mass m/z calcd for $C_{16}H_{30}NaO_4Si$ 337.18111 found 337.1813.

Isomer B was an oil and had: FTIR ($CHCl_3$ cast) 3440 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ -0.02 (s, 6 H), 0.88 (s, 9 H), 1.29-1.47 (m, 3 H), 1.89-1.95 (m, 1 H), 2.02-2.07 (m, 1 H), 2.27-2.36 (m, 1 H), 2.82-2.88 (m, 1 H), 3.08-3.24 (m, 2 H), 3.26 (s, 3 H), 4.26-4.30 (m, 1 H), 4.67 (s, 1 H), 4.76 (*t*, J = 5.9 Hz, 1 H); ^{13}C NMR (C_6D_6, 100 MHz) δ -4.7 (q′), -4.6 (q′), 18.3 (s′), 26.1 (q′), 38.0 (t′), 42.7 (d′), 46.0 (d′), 46.5 (d′), 50.0 (d′), 54.4 (q′), 64.8 (t′), 78.9 (d′), 80.8 (d′), 109.5 (d′); exact mass m/z calcd for $C_{16}H_{30}NaO_4Si$ 337.18111 found 337.1811.

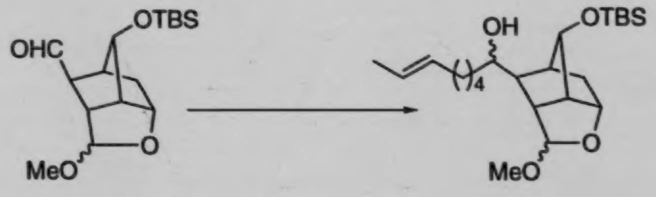
(9-*exo*, 8-*anti*)-8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{3,7}]nonane-9-carbaldehyde (47.7).



47.6 **47.7**

Dess-Martin periodinane (1.80 g, 4.20 mmol) was added to a stirred solution of **47.6** (major isomer) (548.1 mg, 1.75 mmol) and pyridine (4.0 mL, 50 mmol) in CH_2Cl_2 (23 mL), and stirring was continued overnight. The mixture was diluted with CH_2Cl_2 (20 mL) and then washed with a mixture of saturated aqueous $NaHCO_3$ (25 mL) and saturated aqueous $Na_2S_2O_3$ (25 mL). The organic layer was washed with brine (40 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 19 cm), using 1:20 to 1:10 EtOAc-hexanes, gave **47.7** (434.5, 80%) as a solid: mp 32-34 °C; FTIR ($CHCl_3$ cast) 1723 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ -0.10 (s, 3 H), -0.09 (s, 3 H), 0.84 (s, 9 H), 1.17 (d, J = 13.0 Hz, 1 H), 1.64 (d, J = 3.0 Hz, 1 H), 2.06-2.12 (m, 1 H), 2.18-2.26 (m, 1 H), 2.70-2.74 (m, 1 H), 2.78-2.84 (m, 1 H), 3.21 (s, 3 H), 3.98 (s, 1 H), 4.41 (s, 1 H), 4.66-4.69 (m, 1 H), 9.12 (s, 1 H); ^{13}C NMR (C_6D_6, 100 MHz) δ -5.09 (q′), -5.04 (q′), 18.0 (s′), 25.8 (q′), 36.7 (t′), 40.9 (d′), 42.3 (d′), 49.6 (d′), 54.3 (d′ or q′), 54.9 (d′ or q′), 78.3 (d′), 80.5 (d′), 108.8 (d′), 199.3 (d′); exact mass m/z calcd for $C_{16}H_{28}NaO_4Si$ 335.16546 found 335.1658.

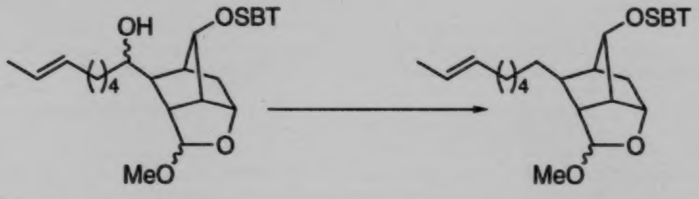
(*E*)-1-[(9-*exo*, 8-*anti*)-8-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-4-oxatricyclo[4.2.1.0^{3,7}]non-9-yl]oct-6-en-1-ol (47.8).



47.7 **47.8**

Potassium (118.7 mg, 3.04 mmol) was added to a suspension of $MgCl_2$ (158.9 mg, 1.63 mmol) in THF (10 mL) and the mixture was stirred and refluxed for 2 h. The resulting dark gray suspension was cooled to room temperature for 0.5 h, and a solution of (*E*)-1-bromo-5-heptene[17] (142.6 mg, 0.81 mmol) in THF (5 mL) was added dropwise at 0 °C over 3 min. Stirring at 0 °C was continued for 1 h, and a portion (10 mL, ca 0.55 mmol) was transferred by syringe to a 50 mL flask cooled to -76 °C. A solution of **47.7** (50.1 mg, 0.160 mmol) in THF (5.0 mL) was added dropwise with stirring to the above solution. Stirring at -76 °C was continued for 5 h, and then saturated aqueous NH_4Cl was added until pH = 5 (pH paper). The mixture was filtered through a pad of Celite (5 x 1 cm) and the pad was washed with EtOAc (40 mL). The organic filtrate was washed with brine (45 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 19 cm), using 1:20 to 1:10 EtOAc-hexanes, gave **47.8** as a single isomer (39.4 mg, 60%) as an oil: FTIR ($CHCl_3$ cast) 3454 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.02 (s, 6 H), 0.88 (s, 9 H), 1.02-1.38 (m, 9 H), 1.58-1.67 (m, 3 H), 1.83-1.89 (m, 1 H), 1.93-2.04 (m, 2 H), 2.31-2.39 (m, 1 H), 2.47-2.53 (m, 1 H), 2.90-2.97 (m, 1 H), 3.13-3.23 (m, 1 H), 3.31 (s, 3 H), 4.50 (s, 1 H), 4.74 (s, 1 H), 4.79-4.75 (m, 1 H), 5.40-5.48 (m, 2 H); ^{13}C NMR (C_6D_6, 125 MHz) δ -4.9 (q′), -4.7 (q′), 18.1 (s′), 18.2 (t′), 25.3 (t′), 26.0 (q′), 29.8 (t′), 32.9 (t′), 36.3 (t′), 38.1 (t′), 44.1 (d′), 45.4 (d′), 50.0 (d′), 52.2 (d′), 54.3 (q′), 73.1 (d′), 79.0 (d′), 80.7 (d′), 109.8 (d′), 125.1 (d′), 131.6 (d′); exact mass *m/z* calcd for $C_{23}H_{42}NaO_4Si$ 433.27501 found 433.2751.

[*tert*-Butyl-[(9-*exo*, 8-*anti*)-5-methoxy-9-[(*E*)-oct-6-enyl]-4-oxatricyclo[4.2.1.0^{3,7}]non-8-yloxy]-dimethylsilane (47.9).



47.8 **47.9**

A solution of MsCl (0.101 mmol) in CH_2Cl_2 (0.7 mL) was added to a stirred and cooled (0 °C) solution of **47.8** (22.9 mg, 0.0559 mmol) and Et_3N (0.10 mL, 0.72 mmol) in CH_2Cl_2 (3.0 mL). The cold bath was left in place, but not recharged, and stirring was continued overnight. The mixture was diluted with EtOAc (30 mL), washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 13.5 cm), using 1:20 to 1:4 EtOAc-hexanes, gave the desired mesylate as an oil.

The mesylate was dissolved in THF (4 mL) and Et_3BHLi (1 M in THF, 0.60 mL, 0.60 mmol) was added with stirring. The resulting solution was refluxed for 1.5 h. Examination by TLC (silica, 1:3 EtOAc-hexane) suggested that ca 50% conversion had occurred. Refluxing was continued for another 8 h and Et_3BHLi (1 M in THF, ca 0.30 mL, ca 0.30 mmol) was added at the beginning of this period and after 2, 4, and 6 h. The reaction mixture was then cooled to room temperature and water (0.5 mL) was added, followed by 3 N NaOH (0.8 mL) and 30% H_2O_2 (1.0 mL). The solution was stirred for 5 min and then diluted with EtOAc (25 mL). The organic layer was washed with brine (20 mL), dried $MgSO_4$ and evaporated. Flash chromatography of the residue over silica gel (2.5 x 17 cm), using 1:20 to 1:4 EtOAc-hexanes, gave **47.9** (12.9 mg, 59% or 71% based on conversion) as an oil and **47.8** (3.9 mg).. Compound **47.9** had: ^1H NMR (C_6D_6, 400 MHz) δ -0.02 (s, 6 H), 0.87 (s, 9 H), 1.03-1.39 (m, 10 H), 1.58-1.64 (m, 3 H), 1.75-1.79 (m, 1 H), 1.92-2.02 (m, 3 H), 2.26-2.33 (m, 1 H), 2.83-2.92 (m, 1 H), 3.27 (s, 3 H), 4.29 (s, 1 H), 4.67 (s, 1 H), 4.75-4.81 (m, 1 H), 5.36-5.45 (m, 2 H); ^{13}C NMR (C_6D_6, 100 MHz) δ -4.9 (q'), -4.8 (q'), 18.1 (q'), 18.2 (s'), 25.9 (q'), 27.9 (t'), 29.5 (t'), 29.8 (t'), 33.0 (t'), 35.2 (t'), 38.1

(t′), 44.0 (d′), 45.4 (d′), 49.5 (d′), 50.1 (d′), 54.2 (q′), 79.1 (d′), 80.6 (d′), 109.5 (d′), 125.0 (d′), 131.8 (d′); exact mass *m/z* calcd for $C_{23}H_{42}NaO_3Si$ 417.28009 found 417.2800.

References

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